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TITLE: Predicting poor outcome Crohn's Disease at the time of first diagnosis

AUTHOR: Gillian Watermeyer (WTRGIL001)

SUPERVISOR: Professor Landon Myer

School of Public Health & Family Medicine, University of Cape Town

Submitted: 11th February 2013

DECLARATION

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For Steve, Sam and Jess

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Abstract

Background and aims

Over time, the majority of patients with Crohn's disease (CD) will develop irreversible gastrointestinal (GIT) damage, notably strictures or fistulas, impacting negatively on quality of life and resulting in hospitalisation and surgery. Early and aggressive drug therapy with immunomodulators (IMMs) and biologics may alter the likelihood of these complications and improve long-term outcomes. However, this approach is extremely expensive and carries its own battery of side-effects such as infections and malignancy. In addition there are a sizable number of patients with CD who will have a benign disease course and never require potent medical therapies or surgical intervention. As a result, there has recently been a surge of interest in early identification of those people who are at risk of developing complicated disease. The aim of our study was thus to identify predictive factors for poor outcome CD in a South African setting, in order to select those who would most benefit from early and aggressive medical therapies.

Methods

A study protocol for a retrospective cohort study of CD patients attending the Inflammatory Bowel Disease clinic at Groote Schuur Hospital (GSH) was drawn up and submitted to the University of Cape Town Ethics Committee. Following approval, an extensive literature review was carried out to identify factors that have been shown to predict poor outcome CD in other populations. Information pertaining to patient demographics, clinical and biochemical factors at first diagnosis and subsequent disease course and complications was extracted. Eligible patients were retrospectively monitored from the time of CD diagnosis until the 31st of December 2011, or alternatively, until the development of predefined endpoints of disabling CD (DCD) or severe CD (SCD). In all cases the patient records were recalled and manually searched to retrieve pertinent information. This study population consisted of CD patients diagnosed between 1980 and 2006 with minimum disease duration of five years and complete data at baseline. Patients were excluded if there was incomplete follow up. Two different definitions of poor outcome CD were evaluated according to predefined criteria: (1) DCD within five years of diagnoses and (2) SCD over the entire disease course. Clinical, demographic, laboratory and biological factors associated with these outcomes were evaluated by univariate and multivariate analysis. For the first part of the study, risk factors for the development of DCD within five years of diagnosis were analysed

using logistic regression analysis. For the second part of the study risk factors at diagnosis associated with time to the development of SCD over the entire disease course were evaluated using Cox proportional hazards analysis.

Results

Complete data was obtained for 120 patients. Seventy two percent developed DCD within 5 years of diagnosis; on multivariate analysis only perianal disease (OR 11.0, 95% CI 1.1-94.7, $p=0.03$) and ileal involvement at diagnosis (OR 5.4, 95% CI 2.1-13.9, $p<0.001$) were predictive. The presence of these two risk factors yielded a sensitivity of 90% and a PPV of 81%. Overall, the rate of SCD was 38% (45/120). On Cox proportional hazards analysis penetrating disease behaviour (HR 2.9, 95% CI 1.2-7.0, $p=0.02$), stricturing disease behaviour (HR 4.6, 95% CI 1.5-14.6, $p=0.01$), perianal disease (HR 3.4, 95% CI 1.6-7.2, $p=0.01$) and the presence of tissue granulomas (HR 2.5, 95% CI 1.3-4.6, $p=0.01$) at diagnosis were independently associated with time to the development of SCD. When analysis was restricted to patients with non-stricturing, non-penetrating CD at diagnosis perianal disease and tissue granulomas were again strongly associated with the time to development of SCD. These two risk factors were highly specific for SCD and yielded a positive predictive value (PPV) of 89%.

Conclusion

At the time of first diagnosis of CD factors predictive of future severe disease were stricturing or penetrating phenotype, perianal disease and tissue granulomas. Patients with these risk factors would most benefit from early and aggressive medical therapies.

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University of Cape Town

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Part A. Study protocol

This protocol was submitted to the Research Ethics Committee of the University of Cape Town. Approval was given on the 20th August 2012.

Protocol approval number: HREC REF: 425/2012. A copy of the approval letter is filed as Appendix 1

1.0 Background and literature review

Crohn's disease (CD) is a form of Inflammatory Bowel Disease (IBD) which may affect any part of the gastrointestinal tract (GIT) in a discontinuous fashion from mouth to anus, most commonly involving the terminal ileum (TI). It is characterised histologically by non-necrotising granulomatous inflammation that is trans-mural in nature. CD is a life-long disorder which may manifest at any time from childhood to late adulthood, most commonly in the late teens and early twenties; with over 80% diagnosed before the age of 40 years. CD is a progressive disorder, the behaviour of which evolves in most patients over time to be complicated by the development of strictures, fistulas or abscesses (Cosnes *et al.* 2011). At diagnosis, more than 80% have purely inflammatory luminal disease, but at 10 years more than half will have progressed to complicated stricturing and fistulising phenotypes, often requiring hospitalisation (Cosnes *et al.* 2002; Louis *et al.* 2001). Ultimately, 80% will undergo surgery (Mekhjian *et al.* 1979). The prevalence of perianal complications also increases with disease duration, from 12% one year after diagnosis to 26% after twenty years (Hellers *et al.* 1980). This disease progression varies enormously between patients; the course can be indolent with prolonged periods of remission, or alternatively it can follow an aggressive, incapacitating path with rapid development of these complications.

Over the past decade, there have been major advances in medications available to treat CD, notably biological therapies such as infliximab and adalimumab which target tumour necrosis factor alpha (TNF). In addition, there has been an evolution in treatment paradigms with conventional immunomodulators (IMMs) such as azathioprine, 6-mercaptopurine and methotrexate now being introduced far earlier in the disease course, in an attempt to change the natural history of CD and improve long-term outcomes (Cosnes *et al.* 2005). It is becoming increasingly apparent that the early and aggressive use of potent therapies such as

biologics and/or IMMs, even at first diagnosis, may potentially modify the progressive and destructive course of CD and result in better outcomes (Colombel *et al.* 2010; D'Haens *et al.* 2008). Consequently, contemporary thinking has shifted in favour of early treatment with the most efficacious therapies available, before the development of irreversible damage and complications, in an attempt to prevent debilitating and disabling CD down the line.

However, such aggressive strategies are not without substantial risk of toxicity and adverse events such as infections and malignancy (Lichtenstein *et al.* 2005; Toruner *et al.* 2008). A major concern when using anti-TNFs in the South African context is the potential risk of disseminated tuberculosis (TB). In addition, population-based studies have shown that a sizable number of CD patients will have a benign course, which means they will never require surgery and never suffer a flare-up severe enough to warrant corticosteroids (Munkholm *et al.* 1995). To subject these individuals to drugs with potentially serious side effects is inappropriate. In addition, these medications (biologics) are extremely expensive and access is limited in resource-challenged environments such as ours. As such, there is a pressing need to identify factors early in the course of CD (ideally at diagnosis) which will help to predict future outcomes and identify those subgroups of patients who will develop poor outcome CD and who will receive greatest benefit from early and aggressive therapy. Equally important is the need to identify people who will likely have a benign course of CD, so as to avoid subjecting them to potentially toxic and unnecessary therapies.

2.0 Study rationale

In light of the potential risk of progression to complicated CD over time, and the lack of local evidence regarding which patients are at risk, the aim of this study is to evaluate the association between clinical and laboratory indices at the time of first diagnosis and subsequent adverse disease outcomes among CD patients receiving care at a tertiary hospital in Cape Town.

Our specific objectives are three-fold:

1. To validate clinical factors at first diagnosis of CD, previously shown in French and Belgian populations to be predictive of a disabling disease course within five years.

2. To explore the association between additional clinical, biochemical and histological factors at diagnosis and the development of disabling CD (DCD) within five years of diagnosis.
3. To explore the association between additional clinical, biochemical and histological factors at diagnosis and time to the development of severe CD (SCD) over the entire disease course.

No other study has been done in South Africa to analyse factors at diagnosis predicting the subsequent development of poor outcome CD. This is an extremely important research question given our limited local access to expensive disease modifying CD medications. Currently anti-TNF therapy is restricted to a total of 14 CD patients in our clinic, less than 3% of our entire CD cohort. Being able to better predict which patients will develop aggressive complicated CD will allow more appropriate use of such scarce resources. In addition we could spare those who will likely have a benign course exposure to medications that place them at risk of active TB, a major concern given that the majority of our clinic patients reside in areas where TB is endemic.

In addition, it is important that this research question is addressed using a local population, as our clinic patients differ from those treated in the West. The most crucial contextual factor is that common genetic CD-susceptibility mutations seen in the developed world are not a feature of CD in our clinic population (Zaahl *et al.* 2005). As such, one questions the generalisability of findings from European cohorts as it is unclear if these would be applicable to South African patients with CD.

3.0 Study Methods

3.1 Study design

A retrospective cohort study will be conducted using an existing database and registry of CD patients attending the IBD clinic at Groote Schuur Hospital (GSH) in Cape Town.

Information pertaining to subject demographics, clinical, biochemical and histological factors at first diagnosis and subsequent disease course and complications will be identified. The patients will be retrospectively followed-up from the time of CD diagnosis until the 31st of December 2011 or alternatively until the development of predefined endpoints of DCD or

SCD or date of death. In all cases the patient case records will be recalled and manually searched to retrieve this information.

This retrospective study design has been chosen as it can potentially answer the research question as efficiently as a prospective study, which is not feasible in our setting. Being able to answer this question would be invaluable in guiding therapy of newly diagnosed CD.

3.2 Study setting/population

The IBD clinic of the Gastro-Intestinal (GIT) unit at Groote Schuur Hospital (GSH), South Africa is to our knowledge the largest dedicated IBD clinic on the African continent. It is a tertiary referral centre which provides care to almost all IBD state patients within the Western Cape; those on medical aid schemes are invariably seen in the private sector but are often referred to GSH in the event of complications. IBD is not managed by primary or secondary care facilities in Cape Town. The clinic only sees patients over the age of 12 years; those younger are seen at the Red Cross Children's Hospital and referred to GSH at the age of 13.

Inclusion criteria

1. A confirmed diagnosis of CD
2. A minimum of five years of follow-up from time of diagnosis

Exclusion criteria

1. Revision of the initial diagnosis to Intestinal TB, Ulcerative colitis or IBD-U (unclassified)
2. Incomplete data at baseline
3. A patient that has not been seen at the clinic within the preceding 12 months
4. The presence of complex perianal disease at diagnosis
5. Surgical resection within one month of diagnosis

The following data will be collected and recorded on an Excel spreadsheet:

At diagnosis

Demographics: age, gender, race, date of CD diagnosis, duration of follow-up

Clinical factors at diagnosis: disease location (as per the Montreal classification: Appendix 3), extent of small bowel involvement (in centimetres), number of colonic segments involved

(ascending colon, transverse colon, descending colon, sigmoid colon and rectum, to a maximum of five), corticosteroid use, family history of IBD, history of appendectomy, smoking status, disease behaviour (as per the Montreal classification: Appendix 3)

Biochemical factors at diagnosis: haemoglobin, white cell count, platelet count, C reactive protein (CRP) and albumin

Histology at diagnosis: the presence or absence of epithelioid granulomas

During follow up

Within five years of diagnosis: further corticosteroid use after diagnosis, further hospitalisation after diagnosis, surgery, creation of a definitive stoma, progression from B1 to B2 or B3 phenotypes (as per the Montreal classification: Appendix 3), IMM use, biologic use

Over the entire disease course: surgical resections, the development of complex perianal fistulas, and creation of a definitive stoma

Definitions

Stricturing disease will be defined as per the Montreal classification as ‘the presence of constant luminal narrowing demonstrated on radiologic, endoscopic or surgical-pathologic methods with pre-stenotic dilatation and/or obstructive signs and symptoms, without the presence of penetrating disease’.

Penetrating disease will be defined as per the Montreal classification as ‘the occurrence of intra-abdominal inflammatory masses, abscesses and/or fistula’. If stricturing and penetrating complications are found simultaneously, the phenotype will be considered as penetrating.

The definition of current smoking will be patients who smoke seven or more cigarettes per week.

Complex perianal disease is defined as per the American Gastroenterology Association recommendation as ‘fistulas that are high intersphincteric, high transsphincteric, extrasphincteric or suprasphincteric, have multiple external openings, are associated with a perianal abscess, fistulise to adjacent organs, are associated with the presence of an anorectal stricture or associated with the presence of active rectal disease’ (Sandborn *et al.* 2003)

3.3 Study endpoints

The two endpoints that will be analysed are:

DCD (as defined by Beaugerie *et al.* 2006): ‘when within five years at least one of the following criteria is present

1. More than two steroid courses required and/or dependence on steroids
2. Further hospitalisation after diagnosis for flare-up or complications of the disease
3. Presence of disabling chronic symptoms (cumulative time of more than 12 months of disabling symptoms: diarrhoea with nocturnal and/ or urgent stools, intense abdominal pain, extra-intestinal manifestations)
4. The need for IMMs
5. Intestinal resection or surgery for perianal disease’

SCD (as defined by Loly *et al.* 2008): ‘any one of the following criteria over the entire disease course

1. The development of complex perianal disease
2. Any colonic resection
3. Two or more small-bowel resections (or a single small-bowel resection measuring more than 50 centimetres in length)
4. The construction of a definitive stoma’

4.0 Statistical analysis

For the first part of the study, the association between all baseline risk factors and the development of DCD within five years of diagnosis will be assessed by univariate analysis. The distribution of all continuous variables will be evaluated and expressed as medians and interquartile ranges (IQR) or means \pm standard deviations (SD) as appropriate. Statistical analysis will employ Chi², Fishers exact, Student t test, Wilcoxon rank sum test or Kruskal-Wallis testing as appropriate. Those variables with *P* values below 0.10 will be further tested in a series of logistic multivariate regression models. The analysis will be performed using STATA version 11 (StataCorp. 2009. *Stata Statistical Software: Release 11*. College Station, TX: StataCorp LP). In the second part of the study, the association with the time to the development of SCD will be assessed by univariate and multivariate analyses using the Cox proportional hazards model. Kaplan-Meier curves will be generated. First, univariate models

will be constructed to produce the crude (unadjusted) hazard ratios for SCD according to the risk factors evaluated. Different models based on different combinations of risk factors will be fitted and compared to select the most clinically relevant and economical model. *P* values less than 0.05 will be considered to be statistically significant. The best model will be validated using the residuals; Cox-Snell residuals to assess overall model fit and Schoenfeld residuals to ensure that the proportional hazards assumption is upheld.

5.0 Ethical considerations

The database that will be used to identify patients has been in existence for over a decade and has given rise to several studies for which Ethical approval has been granted in the past. To ensure subject confidentiality, only the principal investigator will have access to the identity of these patients. Any patient information which may allow identification will not be divulged to any persons and will not appear in the dissertation or any subsequent publications.

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Part B: Literature review

1.0 Introduction

Idiopathic inflammatory bowel disease (IBD) comprises a heterogeneous group of conditions affecting the gastrointestinal tract (GIT). Crohn's disease (CD) and ulcerative colitis (UC) are the two commonest forms of IBD. UC is limited to the colon and is characterised by continuous superficial inflammation. In contrast, CD may affect any part of the GIT in a discontinuous fashion from mouth to anus, most commonly involving the terminal ileum (TI). CD is characterised histologically by non-necrotising granulomatous inflammation that is transmural in nature. CD is a life-long disorder which may manifest at any time from early childhood to late adulthood. Typically, however, CD is diagnosed in the late teens and early twenties, with over 80% before the age of 40 years.

2.0 The natural history of Crohn's disease

CD is a heterogeneous disorder which manifests with diverse clinical phenotypes. These phenotypes are currently defined by the Montreal classification system into sub-categories depending on the age at diagnosis, disease location and disease behaviour (Silverberg *et al.* 2005). This classification is listed in Appendix 3. CD location within the gastrointestinal tract remains relatively constant over time; approximately 20% have isolated CD of the colon, 30% have isolated small bowel involvement while 50% will have CD involving both the ileum and colon. Upper GIT CD is much less common and is seen in less than 10% of cases. Disease behaviour is defined by the presence or absence of intestinal complications such as strictures or fistulas and is categorised as inflammatory non-stricturing, non-penetrating CD (B1), stricturing CD (B2) or penetrating CD (B3). Stricturing disease is also known as stenosing or fibrostenotic disease. Penetrating disease is also known as perforating or fistulising CD and can be complicated by abscess formation.

CD is a progressive disorder and the natural history varies enormously between patients. The course can be indolent with prolonged periods of remission, or alternatively it can follow an aggressive, incapacitating path. In contrast to disease location, CD behaviour evolves in most patients over time. At diagnosis more than 80% have purely inflammatory, non-stricturing

and non-penetrating disease, but at 10 years more than half will have progressed to complicated stricturing and fistulising phenotypes, often requiring hospitalisation (Cosnes *et al.* 2002; Louis *et al.* 2001). Ultimately 80% will undergo surgery (Mekhjian *et al.* 1979). The prevalence of perianal complications also increases with disease duration, from 12% one year after diagnosis to 26% after 20 years (Hellers *et al.* 1980). As such it is clear that CD more often than not, is a chronic, progressive disorder which results in cumulative, irreversible, structural damage to the GIT and the all the complications thereof.

The current burden of IBD in the Western Cape is unclear; the last attempt to measure the magnitude of CD in the greater Cape Town area was in the 1980s (Wright *et al.* 1986). At that time the incidences of CD in the coloured, white and black population groups were calculated to be 1.8, 2.6 and 0.3/100 000 per year respectively. Very likely this incidence will have increased over the past 25 years, a trend that has been noted in both developed and developing countries worldwide (Cosnes *et al.* 2011). This is supported by the large numbers of CD patients treated at our referral tertiary IBD clinic, which cares for approximately 600 individuals with the condition. As such, CD represents an important chronic condition which has far reaching local health and socioeconomic implications.

3.0 The treatment of Crohn's disease

Over the past decade, there have been major advances in medications available to treat CD. This is most notable in the advent of biological therapies, in particular those agents targeting tumour necrosis factor alpha (anti-TNFs) such as infliximab and adalimumab. In addition, there has been an evolution in treatment paradigms as data has emerged on how best to use available therapies in order to improve long term outcomes (Colombel *et al.* 2010). While immunomodulators (IMMs) such as the purine analogues (azathioprine and 6-mercaptopurine) and methotrexate have long been used in CD, the timing of their introduction has changed and they are being introduced far earlier in the disease course, in an attempt to change the natural history of CD (Cosnes *et al.* 2005). It is becoming increasingly apparent that the early and aggressive use of potent therapies such as biologics and/or IMMs, even at first diagnosis, may potentially modify the progressive and destructive course of CD and result in better outcomes (Colombel *et al.* 2010; D'Haens *et al.* 2008). Current thinking has thus shifted towards early treatment with the most efficacious therapies available, before the development of irreversible damage and complications, in an attempt to prevent

debilitating and disabling CD down the line. However, such aggressive strategies are not without substantial risk of toxicity and adverse effects such as infections and malignancy (Lichtenstein *et al.* 2005; Siegel *et al.* 2009; Toruner *et al.* 2008). A major concern when using anti-TNFs in our setting is the potential risk of disseminated tuberculosis (TB). In addition, population based studies have shown that a sizable number of CD patients will have a benign course, never require surgery and never suffer a flare-up severe enough to warrant corticosteroids (Munkholm *et al.* 1995). To subject these individuals to drugs with potentially serious side effects is inappropriate. In addition, these medications (biologics) are extremely expensive and access is limited in resource challenged environments. As such, there is a pressing need to identify factors early in the course of CD (ideally at diagnosis) which will help to predict future outcomes and identify those subgroups of patients who will develop poor outcome CD and who will receive greatest benefit from early and aggressive therapy. It is equally important to identify people who will likely have a benign course of CD, so as to avoid subjecting them to potentially toxic therapies.

4.0 Predicting poor outcome Crohn's disease

Predicting poor outcome CD has been the subject of much interest in Europe and the USA, and several prognostic factors have been identified at the time of diagnosis and used to build predictive models and guide therapeutic decision making. Unfortunately interpreting this data is hindered by the lack of a standardised definition of poor outcome CD, which is subjective and differs between studies (Louis *et al.* 2009; Yarur *et al.* 2011).

The two most commonly cited predictive studies were conducted in referral centres in France and Belgium, reflecting similar populations to our tertiary IBD clinic. In the French Saint-Antoine hospital study of 1188 subjects (Beaugerie *et al.* 2006), the term 'disabling CD' (DCD) encompassed several clinical scenarios within five years of diagnosis; 'the presence of chronic debilitating symptoms, more than two courses of steroids (or steroid dependency), creation of a definitive stoma, further hospitalisation after diagnosis for flare-up or complications of the disease, the need for IMMs, surgery for perianal disease or bowel resection'. In this study, factors at diagnosis that were associated with the development of DCD were the need for corticosteroids (OR: 3.1, 95% CI: 2.2-4.4), an age below 40 years (OR: 2.1, 95% CI: 1.3-3.6), and the presence of perianal disease (OR: 1.8, 95% CI: 1.2-2.8).

The Positive Predictive Value of DCD in patients with 2 and 3 of these predictive factors was 0.91 and 0.93, respectively.

The definition of poor outcome CD used for this analysis has however been criticised as being too broad and as such the second Belgian study of 361 patients (while validating some predictors from the above study using the same definition of DCD described previously) also used a second, more rigid definition (Loly *et al.* 2008). Here, severe CD (SCD) was defined as 'at least two small bowel resections or a small bowel resection of more than 50cm, any colonic resection, a definitive stoma or the development of complex perianal disease at any point during follow up'. Confirming the results of the study by Beaugerie *et al.* (2006), perianal lesions and the need for steroids to treat the first flare, but not age below 40 years, were confirmed as predictive markers for developing DCD at five years. In addition ileocolonic location was a predictor of DCD, a finding also seen on univariate analysis in the Saint-Antoine cohort. Data analysis using the definition of SCD as the outcome, identified stricturing behaviour (HR: 2.1, 95% CI: 1.4-3.2) and weight loss > 5 kg (HR: 1.7, 95% CI: 1.4-2.5) at diagnosis as factors independently associated with the time to development of SCD.

Several other studies have confirmed clinical factors at diagnosis as predictors of poor outcome CD. In the prospective 10-year IBSEN follow-up study (Solberg *et al.* 2007) small bowel location, stricturing disease, penetrating behaviour and age younger than 40 were all found to be independent risk factors for future operative intervention. Upper GIT involvement has also been shown to predict poor outcome CD (Chow *et al.* 2009). Cigarette smoking is an environmental factor known to impact negatively on CD course and is associated with penetrating intestinal complications and the development of fistulas (Latakos *et al.* 2007; Rubin *et al.* 2000).

There are also several laboratory-based predictors of poor outcome CD that have been evaluated. Notably, a number of antibodies against microbial antigens have been described in CD. The most studied are anti-*Saccharomyces cerevisiae* antibody (ASCA), antibody to the outer membrane porin of *Escherichia coli* (anti-OmpC) and antibody against flagellin expressed by Clostridia (anti-CBir1). High titres of these serum antibodies (ASCA, anti-OmpC, and anti-CBir1) correlate with adverse CD outcomes (Vasiliauskas *et al.* 2000; Mow

et al. 2004). Finally, the presence of granulomas on histopathology and mutations of certain genes, notably the nucleotide-binding oligomerization (*NOD2*) gene are also markers of aggressive CD (Heresbach *et al.* 2005; Yarur *et al.* 2011). More recently gene expression profiling of CD8+ T cells was shown to predict a severe course of CD (Lee, *et al.* 2011). In this study there was a substantially increased risk of having relapsing disease in those patients with increased expression of genes involved in antigen-dependent T cell responses.

At present clinical predictors remain the best studied risk factors to guide therapeutic decision making, however it is likely in the future that combinations of both clinical and non-clinical features will allow better prognostication of severe disease. Recently Siegel and colleagues developed a model using system dynamics analysis (SDA) to assess the probability of developing a CD-related complication (Siegel, *et al.* 2011). This model included patient and disease variables, serological markers and medical therapies. Using SDA and Cox analyses they demonstrated how data can be transformed into a simple graph displaying a real-time individualised probability of disease complications and treatment response.

Recently predictors of 15-year CD course were characterized in 600 patients, again from the Saint-Antoine cohort (Cosnes *et al.* 2011). Non-severe evolution was defined as ‘clinically inactive disease for greater than 12 years, less than one intestinal resection without permanent stoma and no death’. Factors independently associated with a non-severe 15-year clinical course were non-smoking status, rectal sparing, high educational level, older age and longer disease duration.

5.0 The value of predicting disease course in CD

The clinical presentation and course of CD progression is markedly heterogeneous; some patients rapidly developing severe, complicated disease, while others have a benign and uncomplicated path. Predicting which patients are at risk for progression to complications, and at what speed, has important implications. Firstly, an accurate prediction will aid in counselling patients and their families on future disease course. Secondly, it is useful in terms of treatment choices as the heterogeneity of CD requires a personalised, tailored approach (Louis *et al.* 2009; Yarur *et al.* 2011). It would be easier to implement aggressive treatment strategies and accept the associated risks if appropriate patients could be identified.

6.0 The value of treating early CD aggressively

There is an emerging body of evidence to suggest that early treatment with IMMs and/or anti-TNFs may modify the natural history of CD. Early use of intensive therapy is often referred to as the top-down (TD) strategy of treatment. This is contrasted with the traditional step-up (SU) strategy where these drugs are only introduced late in the course of the disease when other therapies such as corticosteroids and 5-aminosalicylates have failed (D' Haens *et al.* 2008). Unfortunately, traditional SU algorithms have not impacted the progressive nature of CD to any great extent, and the failure of traditional approaches to alter natural history can in part be attributed to their delayed introduction in advanced disease when complications are already irreversible (Cosnes *et al.* 2005). In contrast a TD approach (or at the very least an accelerated SU strategy) with the early and aggressive use of biologics, with or without IMMS, has been shown to be associated with better clinical outcomes, corticosteroid-free remission rates and the development of fewer complications, hospitalisations and surgical interventions (Colombel *et al.* 2010; D' Haens *et al.* 2008; Feagan *et al.* 2008; Lichtenstein *et al.* 2005). In addition, this strategy is associated with superior endoscopic mucosal healing rates, an outcome which is rapidly becoming a surrogate marker for improving long-term outcomes and is increasingly used in clinical practice (D' Haens *et al.* 2008).

7.0 The potential risks of treating early CD aggressively

In contrast to referral centre studies, analysis of population based cohorts suggests that a sizable subset of CD will run a benign course and never require corticosteroids or surgery (Munkholm *et al.* 1995). To subject these individuals to potentially toxic IMMs or biologic therapies would expose them to unnecessary risk. Thiopurine drugs (azathioprine and 6-mercaptopurine) predispose to serious and opportunistic infections, as well as other possible side effects such as myelotoxicity, hepatotoxicity and pancreatitis. In addition, thiopurine use carries a risk of lymphoma (Kandiel *et al.* 2005; Siegel *et al.* 2009). Another commonly used IMM methotrexate may cause irreversible liver or lung fibrosis, while the anti-TNFs have been associated with an increased risk of infection, notably in our setting tuberculosis. Furthermore, using combinations of these potent therapies increases the potential for complications (Toruner *et al.* 2008). As a result, the early and aggressive use of these drugs in inappropriate patients who will likely experience a benign course of CD imparts unacceptable risk.

8.0 Individual markers to predict the course of CD

Many different demographic, clinical, endoscopic, histologic, serologic, and genetic markers have been evaluated in predicting CD outcomes. Those for which there is evidence demonstrating a role in predicting poor outcome CD will be discussed. These predictors are summarised in Appendix 5.

8.0 Clinical Markers predicting disease course in CD

8.1 Age

Clinical and population-based studies have shown that patients diagnosed with CD at a younger age (<40 years) tend to have more aggressive CD (Beaugerie *et al.* 2006; Solberg *et al.* 2007). Young age is also associated with increased risk of surgery and disease recurrence (Romberg-Camps *et al.* 2009).

8.2 CD behaviour

Perianal disease has emerged as a strong predictor of poor outcome CD in most publications addressing this issue, regardless of how this endpoint was defined (Beaugerie *et al.* 2006; Louis *et al.* 2009; Mekhjian *et al.* 1979). In a Belgian cohort perianal disease was the strongest predictor of severe disease in patients with uncomplicated CD at diagnosis (Loly *et al.* 2008). Moreover perianal disease at diagnosis has been shown to confer a significant risk of developing DCD during 5 years of follow up (Beaugerie *et al.* 2006), as well as being a significant predictor of change in CD behaviour (Tarrant *et al.* 2009). Strictureing disease at diagnosis has also been noted to be a marker of progression to SCD (Loly *et al.* 2008) and subsequent surgery (Solberg *et al.* 2007; Romberg-Camps *et al.* 2009). Penetrating disease behaviour is an additional risk factor predicting a more severe course of CD and the need for surgical intervention (Solberg *et al.* 2007).

8.3 CD Location

When compared to patients with ileal or ileocolonic involvement, patients with CD that is limited to the colon have a lower rate of surgery and are less likely to progress to complicated disease (Solberg *et al.* 2007; Thia *et al.* 2010). Similar findings were reported by Romberg-Camps *et al.* (2009) in that small bowel location was a predictor of future surgery in their long term follow-up study. In addition, a recent study from New Zealand (Tarrant *et al.* 2009)

showed that progression towards complicated disease was more rapid in those with small bowel than colonic disease location. An Asian study (Chow *et al.* 2009) showed that involvement of the upper gastrointestinal tract was an independent predictor of more complicated disease, including hospitalisations.

8.4 Corticosteroids

Patients who require corticosteroid therapy during their first CD flare are more likely to develop DCD during 5 years of follow-up (Beaugerie *et al.* 2006). This was confirmed in another study addressing this same endpoint (Loly *et al.* 2008).

8.5 Smoking

An association between cigarette smoking and CD has long been recognised in that both current and former smoking (and possibly passive smoke exposure during childhood) increases the risk of CD almost 2-fold. In addition, current smoking has been shown to alter the disease course in that smokers with CD are more likely to run a complicated course, to develop stricturing or penetrating disease, to have ileal involvement and to undergo surgery. Smokers with CD also have higher steroid and more immunosuppressant requirements than non-smokers (Latakos *et al.* 2007; Rubin *et al.* 2000).

8.6 Appendicectomy

Studies exploring the association between appendicectomy and CD have reported conflicting findings. A recent meta-analysis demonstrated a significantly increased risk of developing CD within four years following this procedure. This risk diminished to baseline after five years, possibly reflecting misdiagnosis of early CD (Kaplan *et al.* 2008). The effect of a previous appendicectomy on disease course is also controversial with some but not all studies reporting an increased risk for surgical resection and more severe disease when compared to patients who had not undergone appendicectomy (Kaplan *et al.* 2007; Riegler *et al.* 2005).

9.0 Histopathological markers predicting outcome in CD

9.1 Epithelioid granuloma

Epithelioid granulomas are considered a histological characteristic of CD, however in reality only a minority of patients will have them on biopsy specimens. The presence of granulomas has been linked to a more complicated disease course with more extensive ileocolonic and upper gastrointestinal tract involvement and penetrating disease (Freeman 2007). In addition the presence of granulomas may independently predict the need for surgical resection (Heresbach *et al.* 2005).

9.2 Inflammatory Markers

The most commonly used surrogate marker of inflammation in CD is the C-reactive protein (CRP). A rise in CRP often heralds a flare-up of disease and patients with higher levels are more likely to relapse and require corticosteroids (Consigny *et al.* 2006). Although this test is simple to perform, readily available and valuable in assessing inflammatory activity, CRP values have not proven to be good predictors of poor outcome CD. In one Norwegian study (Henriksen *et al.* 2008) there was no association between CRP levels at diagnosis and subsequent risk of surgery. However, in this study a significant association was noted for CRP levels above 53 mg/l in a small sub-group with isolated ileal involvement (OR 6.0, 95% CI 1.1 to 31.9, $p = 0.03$).

9.3 Serological markers

Several studies have shown that serological markers such as ASCA, anti-OmpC and cBir1 antibodies predict CD complications and the need for surgery (Vasiliauskas *et al.* 2000; Mow *et al.* 2004). ASCA in particular has been associated with penetrating disease and early need for surgery. In addition the number and level of antibody response (ASCA, anti-OmpC, and anti-cBir1) correlated with internal penetrating and stricturing disease and the need for surgery in a large paediatric CD cohort (Dubinsky *et al.* 2008).

9.4 Genetic markers

The most studied susceptibility gene in CD is that of the nucleotide-binding oligomerisation domain 2 (*NOD2*). Several common mutations in this gene confer an increased risk of developing CD and have been found to predict the development of small bowel strictures and the need for early surgery. A recent meta-analysis of 49 studies (Adler J, *et al.* 2011) showed that the presence of a single *NOD2* mutation predicted an 8% increase in the risk for complicated disease (B2 or B3), whereas 2 mutations conferred a 41% increase. *NOD2*

mutations did not predict perianal disease ($P = 0.4$) but were associated with the need for surgery (RR 1.6, 95% CI 1.4 – 1.8, $P < 0.001$). Unfortunately the predictive power associated with a single *NOD2* mutation was weak, but the presence of two *NOD2* mutations had 98% specificity for complicated disease (although sensitivity was poor at 11%). Besides *NOD2* other CD susceptibility genes have also been evaluated as prognosticators of poor outcome. Recently a large Dutch study (Weersma *et al.* 2009) evaluated several CD genes; *NOD2*, the IBD5 locus, the Drosophila discs large homologue 5 (*DLG5*), autophagy-related 16-like 1 (*ARG16L1*) and the interleukin 23 receptor (*IL23R*) genes. The authors demonstrated that patients with a severe course of CD had more risk alleles ($p=0.0008$) compared to patients with uncomplicated behaviour (Weersma *et al.* 2009).

9.5 Endoscopic markers

In a French study of CD (Allez *et al.* 2002) with a median follow up of 52 months it was shown that the presence of deep and extensive colonic ulceration was associated with a high risk of colectomy.

9.6 Summary

The ability to predict which patients will develop poor outcome CD and thereby target these individuals with early and aggressive medical therapies would be of great value. An increasing wealth of data has emerged in recent years on predicting prognosis in patients with CD, with a number of clinical, serologic, endoscopic and genetic markers showing promise. Clinical factors, in particular perianal disease and ileal location at diagnosis, seem to be the simplest and most useful to date.

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Part C: Journal “ready” manuscript for submission to the South African Medical Journal

(Instructions for authors are recorded in Appendix 2. As per these instructions references are in the Vancouver style, thus differing from Part A and B)

Abstract

Background and aims

The majority of patients with Crohn's disease (CD) will develop complications in the form of strictures or fistulas over time, impacting negatively on quality of life and resulting in hospitalisations and surgery. Timely drug therapy with immunomodulators and biologics may alter this natural history but carries a significant risk of side-effects. The aim of our study was to indentify predictive factors at diagnosis for poor outcome CD in order to identify those who would most benefit from early, aggressive medical therapies.

Methods

This study included 120 CD patients (diagnosed 1980-2006), with follow-up exceeding 5 years and complete data at baseline. Two different definitions of poor outcome CD were evaluated according to predefined criteria: disabling CD within five years of diagnoses (DCD) and severe CD over the entire disease course (SCD). Clinical, demographic, laboratory and biological factors associated with these outcomes were evaluated by univariate and multivariate analysis.

Results

Seventy two percent (86/120) developed DCD within 5 years of diagnosis; on multivariate analysis perianal disease (OR 11.0, 95% CI 1.1-94.7, $p=0.03$) and ileal involvement at diagnosis (OR 5.4, 95% CI 2.1-13.9, $p<0.001$) were predictive. Overall 38% (45/120) developed SCD and on multivariate Cox proportional hazard analysis penetrating behaviour (HR 2.9, 95% CI 1.2-7.0, $p=0.02$), stricturing behaviour (HR 4.6, 95% CI 1.5-14.6, $p=0.01$), perianal disease (HR 3.4, 95% CI 1.6-7.2, $p=0.01$) and the presence of biopsy granulomas (HR 2.4, 95% CI 1.3-4.6, $p=0.01$) at diagnosis were independently associated with time to the development of SCD. When analysis was restricted to non-stricturing and non-penetrating disease, perianal CD and tissue granulomas remained strongly associated with the development of SCD. These 2 risk factors yielded a specificity of 99% and a positive predictive value of 89%.

Conclusion

At the time of diagnosis, factors predictive of subsequent SCD in our referral centre were stricturing or penetrating phenotype, perianal disease and tissue granulomas.

1.0 Introduction

Crohn's disease (CD) is a chronic disorder with variable clinical manifestations and a heterogeneous disease course. The phenotype of CD is defined by age at diagnosis, location of disease and disease behaviour according to the Montreal classification.¹ Behaviour is subdivided into 'non-stricturing and non-penetrating' (B1), 'stricturing' (B2) and 'penetrating' (B3) disease. The behaviour of CD tends to evolve over time to be complicated by the development of strictures, fistulas or abscesses. At diagnosis more than 80% of patients have purely inflammatory B1 luminal disease, but by 10 years more than half will have progressed to complicated stenosing (B2) and penetrating (B3) phenotypes, often requiring hospitalisation.^{2,3} Ultimately 80% will undergo surgery.⁴

Early and aggressive medical therapy with immunomodulators (IMMS) and biologics may alter this natural history and improve long-term outcomes. However, such strategies place patients at risk of adverse events such as infections and malignancy.^{5,6} In addition, population based studies have shown that a sizable number of CD patients will have a benign course,

never require surgery and never suffer a flare-up severe enough to warrant corticosteroids.⁷ To subject these individuals to drugs with potentially serious side effects is unacceptable. In addition these medications (notably biologics) are expensive and access is limited in resource challenged environments such as ours.

Recently, several studies have analysed factors early in the course of CD which may predict future outcomes and identify those patients at risk of developing complicated CD who would receive greatest benefit from early, aggressive therapy. Equally importantly these factors could identify people who will most likely have a benign course of CD, so as to avoid subjecting them to potentially toxic therapies. In a seminal French study by Beaugerie *et al.* (2006), an initial need for corticosteroids (OR: 3.1, 95% CI: 2.2-4.4), an age below 40 years (OR: 2.1, 95% CI: 1.3-3.6), and the presence of perianal disease (OR 1.8, 95% CI: 1.2-2.8) at diagnosis were associated with the development of disabling CD (DCD) within five years.⁸ The positive predictive value of two or three of these risk factors was 0.91 and 0.93 respectively. A subsequent Belgian study by Loly *et al.* (2008) designed to validate these findings confirmed that perianal lesions at diagnosis and the need for steroids to treat the first flare (but not age below 40 years) were predictive markers for DCD. In addition they demonstrated that ileocolonic location was also associated with DCD (OR 1.74, 95% CI 1.06-2.8).⁹

The definition of poor outcome DCD used in these studies has however been criticized as being too broad and as a consequence three-quarters of study patients had disabling disease, a sub-group too large to target with aggressive medical therapies. As a result Loly *et al.* (2008) used a second, more restrictive definition of severe CD (SCD) which reflected 'clinically significant, non-reversible GIT damage over the entire disease course, characterised by the development of complex perianal disease, any colonic resection, two or more small-bowel resections, a single small-bowel resection of greater than 50 cm or the construction of a definitive stoma'.⁹ The rate of SCD using this definition was 37.4%. Stricturing behaviour (HR: 2.1, 95% CI: 1.4-3.2) and weight loss exceeding 5kgs (HR: 1.7, 95% CI: 1.1-2.5) at diagnosis were independently associated with the time to development of SCD.

To date no study has been done in South Africa to analyse risk factors at diagnosis predicting the subsequent development of poor outcome CD. It is unclear if these forementioned

predictive variables from French and Belgian populations are applicable in our local setting given that our patients differ from those treated in the West. Notably common genetic CD-susceptibility mutations seen frequently in the developed world are not a feature of CD in our clinic population.¹⁰ In light of the potential risk of progression to complicated CD over time, and the lack of local evidence regarding which patients are at risk, the aim of this study was to evaluate the association between clinical and laboratory indices at the time of first diagnosis and subsequent adverse disease outcomes among CD patients receiving care at a tertiary hospital in Cape Town.

2.0 Methods

Patient eligibility

The protocol was approved by the Ethics Committee of the University of Cape Town. Of 567 CD patients registered in our database (up to 31st December 2011) 310 had duration of CD exceeding 5 years. We reviewed the clinical notes of these patients. Patients were excluded if there was incomplete data at baseline, if the initial diagnosis had been subsequently revised, if they had not been seen at the clinic within the preceding year, if there was complex perianal disease at diagnosis or if they had undergone surgical resection within one month of diagnosis. The vast majority of exclusions (80%) were due to missing or unreadable notes or microfilms from the time of initial diagnosis. Details of those excluded are listed in Appendix 4. One hundred and twenty patients were eligible for inclusion.

Study design

This was a retrospective cohort study. Two different definitions of poor outcome CD were evaluated according to predefined criteria:

DCD (as defined by Beaugerie *et al.* 2006)⁸: ‘when within five years at least one of the following criteria is present

1. More than two steroid courses required and/or dependence on steroids
2. Further hospitalisation after diagnosis for flare-up or complications of the disease
3. Presence of disabling chronic symptoms (cumulative time of more than 12 months of disabling symptoms: diarrhoea with nocturnal and/ or urgent stools, intense abdominal pain or extra-intestinal manifestations)

4. The need for IMMs
5. Intestinal resection or surgery for perianal disease

SCD (as defined by Lolly *et al*)⁹: ‘any one of the following over the entire disease course

1. The development of complex perianal disease
2. Any colonic resection
3. Two or more small-bowel resections
4. A single small-bowel resection measuring more than 50 cm in length
5. The construction of a definitive stoma’

Our specific objectives were three-fold:

1. To validate clinical factors at first diagnosis of CD previously shown in French and Belgian populations to be predictive of DCD within five years.
2. To explore the association between additional clinical, biochemical and histological factors at diagnosis and the development of DCD within five years of diagnosis.
3. To explore the association between additional clinical, biochemical and histological factors at diagnosis and time to the development of SCD over the entire disease course

Patients were followed-up from the time of CD diagnosis until the 31st of December 2011 or alternatively until the development of predefined endpoints of DCD or SCD or date of death. The following data was collected and recorded on an Excel spreadsheet.

Demographics: age, gender, race, date of CD diagnosis, duration of follow-up

Clinical factors at diagnosis: disease location (as per the Montreal classification), extent of small bowel involvement (in centimetres), number of colonic segments involved (ascending colon, transverse colon, descending colon, sigmoid colon and rectum, maximum of five), corticosteroid use, family history of IBD, history of appendicectomy, smoking status (patients were considered current smokers if ≥ 7 cigarettes per week, disease behaviour (as per the Montreal classification)

Biochemical factors at diagnosis: haemoglobin, white cell count, platelet count, C- reactive protein (CRP), and albumin. These markers were considered as normal or abnormal according to the reference range

Histology at diagnosis: the presence or absence of tissue granulomas

Within five years of diagnosis: further corticosteroid use after diagnosis, further hospitalisation after diagnosis, surgery, creation of a definitive stoma, progression from B1 to B2 or B3 phenotypes (as per the Montreal classification), IMM use, biologic use

Over the entire disease course: surgical resections, the development of complex perianal fistulas, and creation of a definitive stoma

3.0 Statistical analysis

For the first part of the study the association between all baseline risk factors and the development of DCD within five years of diagnosis was assessed by univariate analysis. All continuous variables evaluated were not normally distributed and are thus expressed as medians and interquartile ranges (IQR). Categorical variables were compared using the Chi² or the Fisher exact test when appropriate. Those variables with *P* values below 0.10 were further tested in a series of logistic multivariate regression models. For the second part of the study univariate and multivariate Cox proportional hazard analysis was used to identify risk factors at diagnosis that were associated with time to the development of SCD during follow-up. The proportional hazards assumption for specific predictor variables was checked and a departure from this assumption was not noted for any of the predictor variables. The Kaplan-Meier method was used to estimate the cumulative probability (1 minus survival-free) of SCD as well as progression from B1 to B2 or B3 phenotypes over time.

4.0 Results

The case records of patients diagnosed with CD at Groote Schuur Hospital between 1980 and 31st December 2006 were retrospectively reviewed. Overall 120 were deemed eligible for study inclusion. Sixty percent (72/120) of the cohort were female. The median age at diagnosis was 31 years (IQR 23-40). The majority of study participants were of 'cape coloured' ancestry (76%, 91/120), 18% (22/120) were caucasian and 6% (7/120) black. At diagnosis 40 % (48/120) had isolated ileocaecal (L1) disease, 26% (31/120) isolated colonic

(L2) disease and 34% ileocolonic (L3) disease (41/120). Five percent (6/120) also had involvement of the upper GIT. At diagnosis disease behaviour was classified as non-stricturing, non-penetrating (B1) in 84% (101/120), stricturing (B2) in 6% (7/120) and penetrating (B3) in 10% (12/120). Thirteen percent (16/120) had evidence of perianal disease. Sixty five percent (78/120) were active cigarette smokers at the time of diagnosis. Fifty four percent (65/120) were treated with corticosteroids for the first flare of disease.

The development of DCD

Overall 72% (86/120) developed DCD within five years of diagnosis. The median time to the development of DCD was 12 months (IQR 5-24). Univariate analysis of all baseline parameters was performed and the results of these are presented in Tables 1 and 2.

At diagnosis the presence of perianal disease, a history of more than five kilogram weight loss and small bowel involvement exceeding 20cm were significantly associated with the development of DCD within five years. Isolated colonic involvement at diagnosis (L2) appeared to confer protection against developing DCD when compared to other locations (L1 or L3). In contrast, age at diagnosis, smoking status, use of steroids for the 1st flare and disease behaviour were not significantly associated with the development of DCD. None of the laboratory or histological parameters evaluated at diagnosis predicted the development of DCD within five years. On multivariate analysis only perianal disease (OR 11.0, 95% CI 1.1-94.7, $p=0.03$) and ileal (L1 or L3) involvement at diagnosis (OR 5.4, 95% CI 2.1-13.9, $p<0.001$) were significantly associated with the development of DCD within five years. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the model including these two risk factors were 90%, 47%, 81% and 64%, respectively. The area under the receiver operating characteristic (ROC) curve was 0.72.

The development of SCD

Overall 38% (45/120) of patients developed SCD over their disease course. The median time to the development of SCD was 36 months (IQR 11-76). The Kaplan-Meier method was used to calculate the cumulative probability of SCD, which was 11.7%, 25.3% and 35.1% at 1, 5, and 10 years after diagnosis respectively. Kaplan-Meier curves for the development of SCD are shown in Figure 1. Clinical, laboratory and histological predictors at diagnosis associated with the time to development of SCD are presented in Tables 3 and 4. After multivariate analysis, only penetrating disease behaviour (HR2.9, 95% CI 1.2-7.0, $p=0.02$), stricturing

disease behaviour (HR 4.6, 95% CI 1.5-14.6, $p=0.01$), perianal disease (HR 3.4, 95% CI 1.6-7.2, $p=0.01$) and the presence of granulomas (HR 2.4, 95% CI 1.3-4.6, $p=0.01$) at diagnosis were independently associated with time to the development of SCD.

B1 disease at diagnosis

Overall 34% (34/101) of patients with purely B1 phenotype at diagnosis developed SCD. The median time to the development of SCD was 43 months (IQR 11-96). On multivariate Cox analysis risk factors at diagnosis that were significantly associated with time to the development of SCD were perianal disease (HR 2.8, 95% CI 1.3-6.0, $p=0.01$) and the presence of tissue granulomas (HR 2.2, 95% CI 1.1-4.4, $p=0.03$).

Kaplan-Meier curves for the development of SCD according to the presence or absence of these 2 factors are shown in Figure 2. Sensitivity, specificity, PPV and NPV of a logistic regression model including these two risk factors were 21%, 99% and 88% and 71%, respectively. The area under the ROC curve was 0.68.

Overall 43% (43/101) patients with B1 disease at diagnosis progressed to B2 or B3 phenotype over time. The cumulative probability of developing either of these was 13% at 1 year, 24% at 2 years, 33% at 5 years, 43% at 10 years and 68% at 20 years. The median time to progression was 24 months (IQR 11-78). None of the baseline parameters assessed was significantly associated with time to B2/B3 progression.

Forty patients (40%) with B1 phenotype at diagnosis ultimately required a surgical resection, while 26 (26%) underwent 2 or more surgical resections. Granulomas at diagnosis was the only predictor for more than one surgical procedure during follow up (OR 4.7; 95% CI 1.8-12.3, $p=0.002$).

5.0 Discussion

Our results are consistent with previous reports in that the majority of CD patients had uncomplicated non-penetrating, non-stricturing CD at initial diagnosis and the majority went on to a disabling disease course over time. Seventy two percent of our cohort developed DCD within 5 years of diagnosis, similar to the 85.2% and 57.9% reported by Beaugerie *et al* and Loly *et al* respectively.^{8,9} As was shown in their studies the presence of perianal lesions at baseline was predictive. However other variables such as the need for corticosteroids for the

first flare and age less than 40 years were not shown to be associated with an increased risk in our cohort. This may reflect our much smaller sample size than those in the forementioned studies. We also showed that ileal involvement at diagnosis is predictive of DCD while isolated colonic disease is protective. This concurs with data from the large population-based IBSEN Scandinavian cohort study which showed that ileal location was associated with future surgical resection, a finding validated in a Maastricht population-based cohort.^{11,12} In addition, a study from New Zealand has shown that progression towards complicated disease was more rapid in those with small bowel than colonic disease location ($P < 0.001$).¹³

The very high proportion of patients developing DCD in our study echoes the loose definition of this outcome, making it somewhat impractical in guiding therapeutic decision-making. The more restrictive end-point of SCD defined by Loly *et al.*, reflecting non-reversible and clinically significant damage, is likely to be more meaningful in assessing the risks and benefits of early, aggressive therapy.⁹ Overall 38% of our cohort developed SCD over their disease course. This is almost identical to that reported by Loly *et al.* in their Liège cohort.⁹ We found that perianal disease, penetrating or stricturing behaviour and granulomas at diagnosis were associated with earlier development of SCD. Several publications have also identified stricturing or penetrating CD phenotype at diagnosis as predictors of poor outcome. Loly *et al.* showed a strong association between stricturing disease at diagnosis and time to development of SCD (HR: 2.1, 95% CI: 1.4-3.2).⁹ In the previously mentioned Maastricht cohort, stricturing lesions were predictive of first surgery in 476 patients with a mean follow-up of 7 years, a finding also noted in the IBSEN study.^{11,12} In addition the IBSEN data showed an association between penetrating disease and time to first surgery.¹²

When considering our patients with uncomplicated non-stricturing, non-penetrating disease (B1) at diagnosis, perianal lesions and granulomas were again associated with an unfavourable outcome. Perianal disease has emerged as a strong predictor of poor outcome CD in most publications addressing this issue, regardless of how this endpoint was defined. In the study by Loly *et al.* perianal disease was the strongest predictor of SCD in patients with uncomplicated disease at diagnosis.⁹ The previously mentioned New Zealand study also showed that perianal disease was a significant predictor of change in CD behaviour over time (HR: 1.62, $P < 0.001$).¹³ It is unclear how perianal disease may predispose to poor-outcome CD but this association may reflect a genetic susceptibility. Recently an Italian study has

shown an association between polymorphisms in a known CD susceptibility gene, the IRGM (immunity-related GTPase) gene, and the risk of perianal fistulising CD.²⁰ Polymorphisms in this gene also predicted the development of complicated CD.²⁰

Epithelioid granulomas are considered a histological characteristic of CD, however in reality only 15–25% of patients will have them on biopsy specimens and their pathogenesis is unknown. Only a few studies evaluating poor outcome CD have included granulomas in analysis. A study by Freeman showed that the presence of granulomas was linked to a more complicated disease course, with more extensive ileocolonic and upper gastrointestinal tract involvement and penetrating disease.¹⁴ In addition the presence of granulomas may independently predict the need for surgical resection¹⁵ and in our study granulomas at diagnosis was the only predictor for more than one surgical procedure during follow up. It is unclear how granulomas may influence CD outcome however one possible explanation is an association with autophagy genetic variants. Autophagy is a process involved in the elimination of intracellular bacteria and this pathway appears altered in CD. Reduced clearance of pathogenic bacteria might drive the chronic inflammation observed in these patients. Genetic variants in autophagy genes ATG16L1 (autophagy-related gene 16-like 1) and IRGM (immunity-related GTPase M) have been associated with susceptibility to CD. A recent study from Leuven evaluated surgical specimens from 464 CD patients and found associations between granulomas and several autophagy gene variants. In addition this study showed that granulomas were predictive of aggressive CD.¹⁶

In contrast to our study findings, Loly *et al.* showed that weight loss exceeding five kilograms at diagnosis was a predictor of SCD. Interestingly when they restricted their analysis to patients with B1 disease at diagnosis this was no longer significant, suggesting that weight loss was associated with complicated CD at diagnosis and not a predictor of SCD in its own right.⁹

Our study has a number of limitations. Firstly, we excluded patients with missing or incomplete data at diagnosis. This accounted for 80% of exclusions and was largely due to missing or unreadable microfilms documenting the initial consultation, incomplete note taking by the diagnosing physician or unavailable blood results. As such baseline characteristics (to determine if they differed from study patients who were included) were difficult to obtain in these individuals. This is a potential source of bias; however it is likely

that this data was missing at random and not correlated with CD severity or outcome. In addition, the cumulative probabilities of progressing from B1 disease at diagnosis to stenosing or penetrating phenotypes over time is almost identical to those reported in a large population based study from Olmsted County, Minnesota.¹⁷ Furthermore, baseline demographics (age and gender) as well as disease location and behaviour of our study participants were very similar to that reported in a large New Zealand population-based CD cohort, with the exception that many more of our patients were active smokers at diagnosis.¹³ Another potential source of bias is that only patients with complete follow up data were included. This could introduce selection bias as patients lost to follow up may have less severe disease than those who continued to be seen in our clinic. A further possible bias is that ours is a referral centre and our clinic patients may have more aggressive CD than those seen at other hospitals. However, the percentage of patients treated with corticosteroids for the first flare-up (54%) was very similar to that in a large North European population-based study.⁷ Another potential confounding factor in our study is the ethnic distribution of our cohort, which differs from that of the Western Cape population. In the 2011 national census 48.8% of people in the Western Cape described themselves as 'coloured', 32.8% as 'black', 15.7% as 'white', and 1.0% as 'asian'.²¹ In our cohort the vast majority (76%) of subjects were coloured. This notable difference from the demographics of the general population may reflect a discord in medical care provision as a consequence of the Apartheid system, whereby white South Africans had better access than other racial groups to private health care; resulting in the majority of patients attending state institutions such as ours being of non-white ethnicity. An additional study limitation is that we did not evaluate serological, endoscopic or genetic predictors of poor outcome as these are not routinely tested in our clinic. Finally our study population was relatively small and could have been underpowered to detect significant associations for some of the baseline factors which may be predictive of poor outcome CD.

Despite these limitations our study has provided some valuable information, notably this is the first South African study to identify predictors of poor outcome CD. This will aid the decision in our setting when to risk aggressive medical therapies early in the disease course. As emphasised by Louis *et al* in a recent review there are two possible errors in managing CD: over treating patients who will have benign disease and under treating those who will go on to develop poor outcomes.¹⁹ Most patients who have stricturing or penetrating phenotypes

at diagnosis would already be considered complicated and thus candidates for aggressive therapy with IMMs and biologics.¹⁸ As such, predicting poor outcome CD in these patients is not as valuable as in patients with uncomplicated disease. Here, the decision to start disease modifying therapies has far more important consequences. In our study perianal disease and granulomas at diagnosis were very specific for the development of SCD over the disease course. Only 1% of individuals with these two predictors at diagnosis would be falsely classified as having SCD and thus subjected to aggressive therapies unnecessarily. In addition these two risk factors are routinely assessed at baseline and do not require expensive blood testing or genetic analysis.

6.0 Conclusion

Data from this retrospective study has shown that 72% of our cohort developed DCD within five years of diagnosis. This proportion is too high to use predictive factors at diagnosis to guide therapeutic algorithms. However using the more restrictive definition of SCD 38% of our cohort developed poor outcome CD over their disease course, a more clinically appropriate endpoint to target. Our study has identified several factors at diagnosis predictive of this outcome. Notably perianal disease and granulomas were independently associated with time to the development of SCD in patients with uncomplicated CD at diagnosis. The PPV of these two risk factors at diagnosis is 88% and the specificity 99%.

Table 1: Demographic and clinical predictors of DCD at diagnosis: univariate analysis

Disease course within 5 years of diagnosis			
Predictors at diagnosis*	Disabling CD N =86 (%)	Non-disabling CD N =34 (%)	p
Female gender	49/86 (57%)	23/34 (68%)	0.28
Race			0.92
White	15/86 (17%)	7/34 (21%)	
Black	5/86 (6%)	2/34 (6%)	
Coloured	66/86 (77%)	25/34 (74%)	
Age*	31 (23-38)	32 (24-41)	0.44
Age			0.87
A1, <17	7/86 (8%)	2/34 (6%)	
A2, 17-40	59/86 (69%)	23/34 (68%)	
A3, >40	20/86 (23%)	9/34 (26%)	
Behaviour			0.17
B1	69/86 (80%)	32/34 (94%)	
B2	6/86 (7%)	1/34 (3%)	
B3	11/86 (13%)	1/34 (3%)	
Perianal disease	15/86 (17%)	1/34 (3%)	0.04
Location			0.004
L1	39/86 (45%)	9/34 (26%)	
L2	15/86 (18%)	16/34 (47%)	
L3	32/86 (37%)	9/34 (27%)	
Extent of SB in cm*	10 (5-20)	5 (0-10)	0.002
Extent of SB>20cm	28/86 (33%)	4/34 (12%)	0.02
Number of colonic segments involved*	1 (0-3)	3 (0-4)	0.09
Upper GIT involvement	4/86 (5%)	2/34 (6%)	0.55
Rectal involvement	12/86 (14%)	7/34 (21%)	0.37
IBD Family history	8/86 (9%)	3/34 (9%)	0.62
Current smoker	58/86 (67%)	20/34 (59%)	0.37
Past appendectomy	9/86 (11%)	1/34 (3%)	0.17
> than 5kg weight loss	55/86 (64%)	14/34 (41%)	0.02
Steroids for 1 st flare	45/86 (52%)	20/34 (59%)	0.52
Extra-intestinal manifestations	20/86 (23%)	8/34 (24%)	0.98

*All continuous variables are recorded as medians (IQR)

Table 2: Laboratory and histological predictors of DCD at diagnosis

	Disabling CD N=86	Non-disabling CD N=34	p
Haemoglobin*	11.95 (10.3-12.6)	12 (10.5-12.8)	0.96
White cell count*	10.43 (7.2-13.95)	10 (\pm 6.23-14)	0.36
Platelet count*	430.5 (333-538)	395(313-504)	0.6
Serum albumin*	35.5 (33-41)	35.5 (32-39)	0.96
Ferritin*	50 (33-74)	69 (63-88)	0.31
CRP*	27.5 (12-62)	36 (12-65)	0.82
Granulomas	38/86	12/34	0.37

*All continuous variables are recorded as medians (IQR)

University of Cape Town

Figure 1: Kaplan-Meier curves for the development of SCD

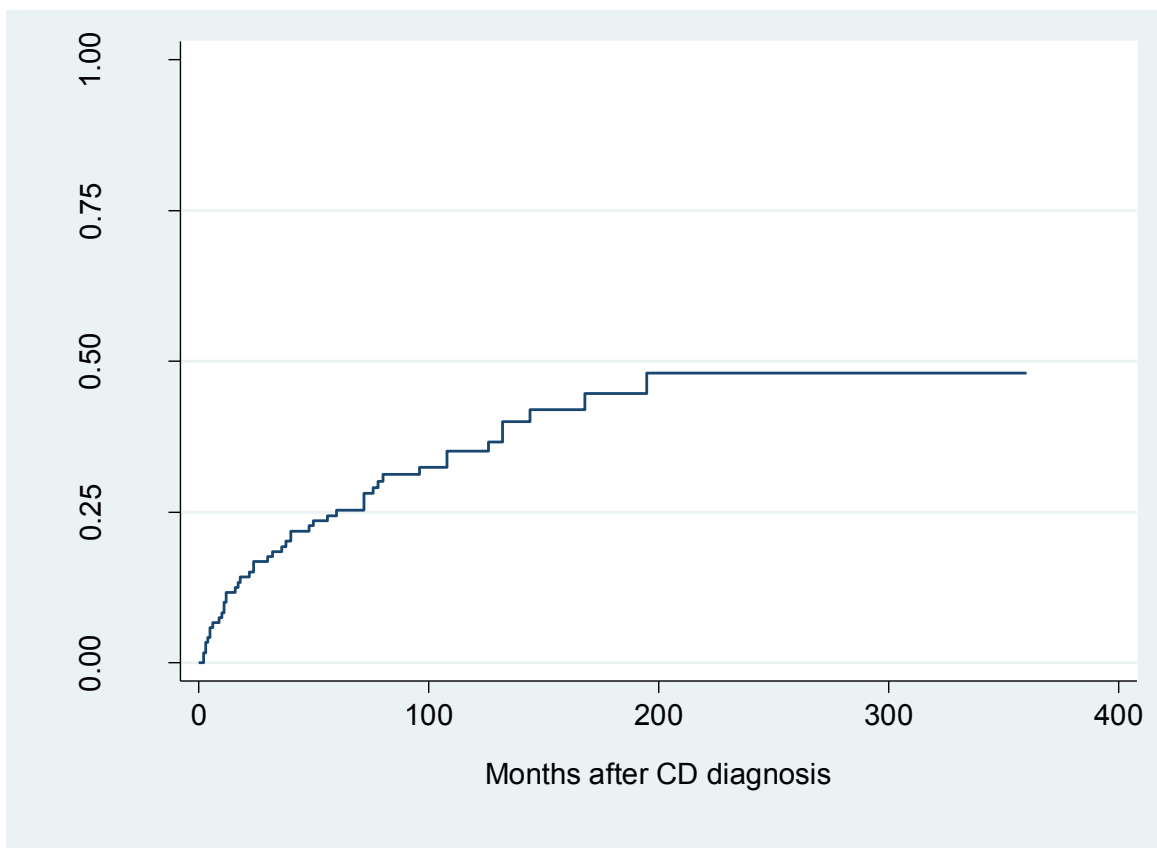


Figure 2: Kaplan-Meier curves for the development of SCD according to the presence or absence of perianal disease and granulomas at diagnosis in patients with B1 phenotype

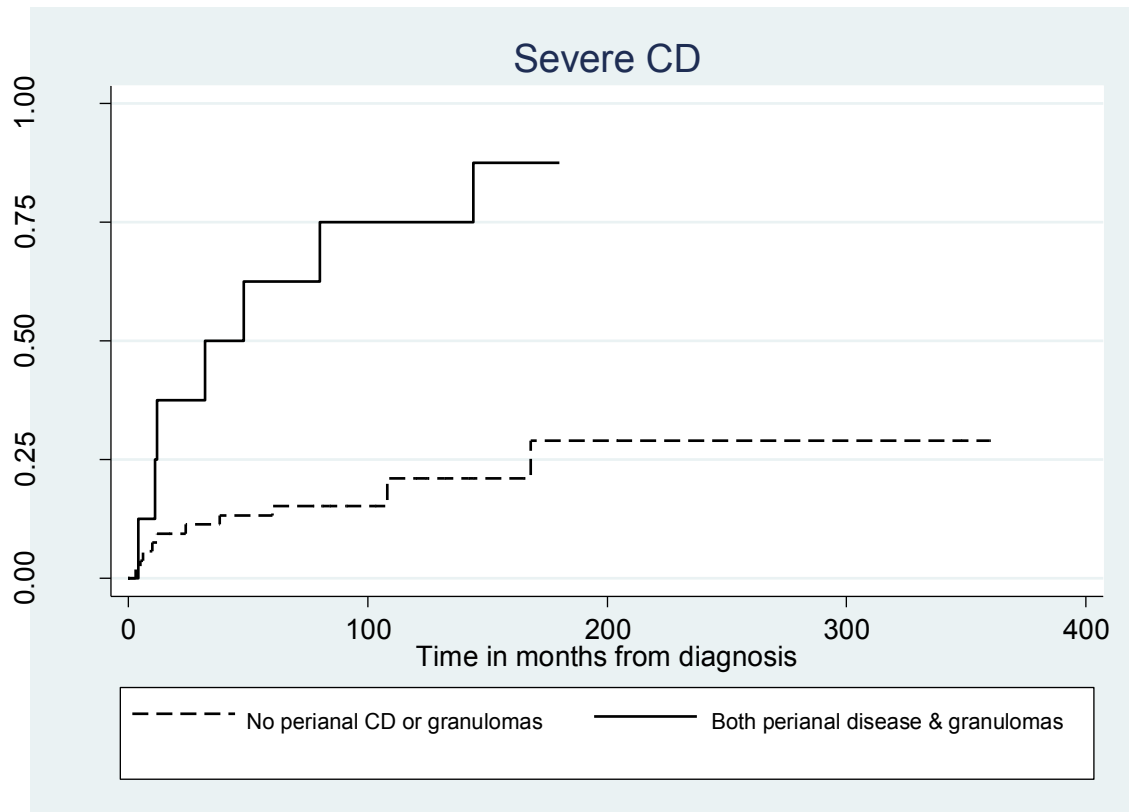


Table 3 Clinical and demographic risk factors at diagnosis significantly associated with time to development of SCD, analysed with Cox proportional hazard method

Risk factors at diagnosis	Non-severe N=75 (%)	Severe CD N=45 (%)	Unadjusted			Adjusted		
			HR	95% CI	p	HR	95% CI	p
Female gender	50/75(67%)	22/45 (49%)	0.56	0.31-1.0	0.05	0.59	0.32-1.1	0.1
Race						Not included		
White	14/75 (19%)	8/45 (18%)	1	Ref	0.98			
Black	5/75 (7%)	2/45 (4%)	0.75	0.16-3.55				
Coloured	55/75 (73%)	35/45 (78%)	0.98	0.46-2.12				
Age								
A1, <17	4/75 (5%)	5/45 (11%)	1	Ref	0.20	1	Ref	
A2, 17-40	50/75 (67%)	32/45 (71%)	0.60	0.23-1.55		0.48	0.18-1.32	0.16
A3, >40	21/75 (28%)	8/45 (18%)	0.45	0.15-1.39		0.43	0.13-1.41	0.16
Behaviour								
B1	67/75 (89%)	34/45 (76%)	1	Ref	0.006	1	Ref	
B2	3/75 (4%)	4/45 (9%)	2.29	0.81-6.49		4.62	1.46-14.61	0.01
B3	5/75 (7%)	7/45 (16%)	2.89	1.26-6.66		2.93	1.23-7.0	0.02
Perianal disease	5/75 (7%)	11/45 (24%)	3.05	1.54-6.04	0.001	3.44	1.63-7.24	0.001
Location						Not included		
L1	27/75 (36%)	21/45 (47%)	1	Ref	0.80			
L2	23/75 (31%)	7/45 (16%)	0.63	0.28-1.42				
L3	25/75 (33%)	16/45 (36%)	0.94	0.49-1.81				
Extent of SB>20cm	25/75 (20%)	17/45 (38%)	1.78	0.97-3.27	0.03	1.01	0.99-1.03	0.16
Colonic segments involved	2 (0-3)	1 (0-3)	0.94	0.8-1.11	0.45	Not included		
Upper GIT	3/75 (4%)	3/45 (7%)	1.32	0.41-4.28	0.65	Not included		
Rectal involvement	13/75 (17%)	6/45 (13%)	0.8	0.34-1.89	0.61	Not included		
Family history	6/75 (8%)	5/45 (11%)	1.49	0.59-3.78	0.41	Not included		
Current smoker	51/75 (68%)	27/45 (60%)	0.65	0.36-1.18	0.80	Not included		
Appendectomy	5/75 (7%)	5/45 (11%)	1.39	0.55-3.52	0.49	Not included		
> than 5kg weight loss	37/75 (49%)	32/45 (71%)	2.15	1.12-4.1	0.02	1.18	0.9-3.45	0.1
Steroids	41/75 (55%)	24/45(53%)	1.08	0.6-1.94	0.80	Not included		
EIM*	19/75 (25%)	9/45 (20%)	0.7	0.33-1.45	0.33	Not included		

*Extra-intestinal manifestations; HR: hazards ratio, 95% CI: 95% confidence interval

Table 4 Laboratory and histological parameters at diagnosis associated with time to development of SCD, analysed with Cox proportional hazard method

Risk factors at diagnosis	Non-severe N=75 (%)	Severe CD N=45 (%)	Unadjusted			Adjusted		
			HR	95%CI	p	HR	95% CI	p
Haemoglobin*	56/75 (75%)	37/45 (82%)	1.55	0.72-3.34	0.26	Not included		
White cell count†	34/75 (45%)	26/45 (58%)	1.39	0.77-2.52	0.27	Not included		
Platelet count †	48/75 (64%)	28/45 (62%)	1.19	0.65-2.18	0.57	Not included		
CRP †	63/75 (84%)	40/45 (89%)	0.77	0.28-2.18	0.63	Not included		
Albumin*	27/75 (36%)	18/45 (40%)	1.18	0.65-2.14	0.60	Not included		
Granulomas	24/75 (32%)	26/45 (58%)	2	1.12-3.66	0.02	2.39	1.25-4.59	0.009

*Treated as a categorical variable: within the normal reference range or below the normal reference range

†Treated as a categorical variable: within the normal reference range or above the normal reference range

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Appendix 1: Ethics approval

HREC Ref: 425/2012 – 20Aug2012

UNIVERSITY OF CAPE TOWN



Faculty of Health Sciences
Human Research Ethics Committee
Room E52-24 Grootte Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6338 • Facsimile [021] 406 6411
e-mail: shuretta.thomas@uct.ac.za

20 August 2012

HREC REF: 425/2012

Dr G Watermeyer
c/o A/Prof L Myer
E23, GIT Unit
NGSH

Dear Dr Watermeyer

PROJECT TITLE: PREDICTING POOR OUTCOME CROHN'S DISEASE AT THE TIME OF DIAGNOSIS

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

It is a pleasure to inform you that the HREC has **formally approved** the above mentioned study.

Approval is granted for one year till the 30th August 2013

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

(Forms can be found on our website: www.health.uct.ac.za/research/humanethics/forms)

Please note that permission must be obtained from GSH to access patient records for this retrospective review.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the HREC REF in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN ETHICS
Federal Wide Assurance Number: FWA00001637.

Institutional Review Board (IRB) number: IR500001938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical

s.tbomas

Appendix 2: South African Medical Journal Author Guidelines

AUTHORSHIP

Named authors must consent to publication. Authorship should be based on substantial contribution to: (i) conception, design, analysis and interpretation of data; (ii) drafting or critical revision for important intellectual content; and (iii) approval of the version to be published. These conditions must all be met (uniform requirements for manuscripts submitted to biomedical journals; refer to www.icmje.org).

CONFLICT OF INTEREST

Authors must declare all sources of support for the research and any association with a product or subject that may constitute conflict of interest.

RESEARCH ETHICS COMMITTEE APPROVAL

Provide evidence of Research Ethics Committee approval of the research where relevant.

PROTECTION OF PATIENT'S RIGHTS TO PRIVACY

Identifying information should not be published in written descriptions, photographs, and pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) gives informed written consent for publication. The patient should be shown the manuscript to be published. Refer to www.icmje.org.

ETHNIC CLASSIFICATION

References to ethnic classification must indicate the rationale for this.

MANUSCRIPTS

Shorter items are more likely to be accepted for publication, owing to space constraints and reader preferences.

Research articles (previously 'Original articles') not exceeding 3 000 words, with up to 6 tables or illustrations, are usually observations or research of relevance to clinical medicine and related fields. References should preferably be limited to no more than 15. Please provide a structured abstract not exceeding 250 words, with the following recommended headings: *Background, Objectives, Methods, Results, and Conclusion.*

MANUSCRIPT PREPARATION

Qualification, affiliation and contact details of ALL authors must be provided in the manuscript and in the online submission process.

Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.

Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dl). Litres are denoted with a lowercase 'l' e.g. 'ml' for millilitres). Units

should be preceded by a space (except for %), e.g. '40 kg' and '20 cm' but '50%'.

Greater/smaller than signs (> and <) should be placed immediately preceding the relevant number, i.e. 'women >40 years of age'. The same applies to ± and °, i.e. '35±6' and '19°C'.

Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160...

Quotes should be placed in single quotation marks: i.e. the respondent stated: '...'

Round **brackets** (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.

General formatting

The manuscript must be in Microsoft Word or RTF document format. Text must be single-spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes, with the exception of Tables).

ILLUSTRATIONS AND TABLES

If tables or illustrations submitted have been published elsewhere, the author(s) should provide consent to republication obtained from the copyright holder.

Tables may be embedded in the manuscript file or provided as '**supplementary files**'. They must be numbered in Arabic numerals (1,2,3...) and referred to consecutively in the text (e.g. 'Table 1'). Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged. Tables must be cell-based (i.e. not constructed with text boxes or tabs), and accompanied by a concise title and column headings. Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'. Figure legends: Fig. 1. 'Title...'

All illustrations/figures/graphs must be of **high resolution/quality**: 300 dpi or more is preferable, but images must not be resized to increase resolution. Unformatted and uncompressed images must be attached individually as '**supplementary files**' upon submission (not solely embedded in the accompanying manuscript). TIFF and PNG formats are preferable; JPEG and PDF formats are accepted, but authors must be wary of image compression. Illustrations and graphs prepared in Microsoft Powerpoint or Excel must be accompanied by the original workbook.

REFERENCES

Authors must verify references from the original sources. *Only complete, correctly formatted reference lists will be accepted.* Reference lists must be generated manually and **not** with the use of reference manager software.

References should be inserted in the text as superscript numbers, e.g. These regulations are

endorsed by the World Health Organization,² and others.^{3,4,6}

All references should be listed at the end of the article in numerical order of appearance in the **Vancouver style** (not alphabetical order). Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus.

Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al. First and last page, volume and issue numbers should be given.

Wherever possible, references must be accompanied by a digital object identifier (DOI) link and PubMed ID (PMID)/PubMed Central ID (PMCID). Authors are encouraged to use the DOI lookup service offered by **CrossRef**.

Journal references:

Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. *Stat Med* 1998;289:350-355. [<http://dx.doi.org/10.1000/hgjr.182>] [PMID: 2764753]

Book references:

Jeffcoate N. *Principles of Gynaecology*. 4th ed. London: Butterworth, 1975:96-101.

Chapter/section in a book:

Weinstein L, Swartz MN. Pathogenic properties of invading microorganisms. In: Sodeman WA jun, Sodeman WA, eds. *Pathologic Physiology: Mechanisms of Disease*. Philadelphia: WB Saunders, 1974:457-472.

Internet references:

World Health Organization. *The World Health Report 2002 - Reducing Risks, Promoting Healthy Life*. Geneva: World Health Organization, 2002. <http://www.who.int/whr/2002> (accessed 16 January 2010).

Other references (e.g. reports) should follow the same format:

Author(s). Title. Publisher place: publisher name, year; pages.

Cited manuscripts that have been accepted but not yet published can be included as references followed by '(in press)'.

Unpublished observations and personal communications in the text must not appear in the reference list. The full name of the source person must be provided for personal communications e.g. '...(Prof. Michael Jones, personal communication)'.

Appendix 3

Classification of Crohn's Disease according to the Montreal Classification

Age at diagnosis

A1: 16 yr and under

A2: 17–40 yr

A3: Over 40 yr

Location

L1: Ileal

L2: Colonic

L3: Ileocolonic

L4: Isolated upper GIT

Behaviour

B1: Non-stricturing, non-penetrating (inflammatory)

B2: Stricturing

B3: Penetrating

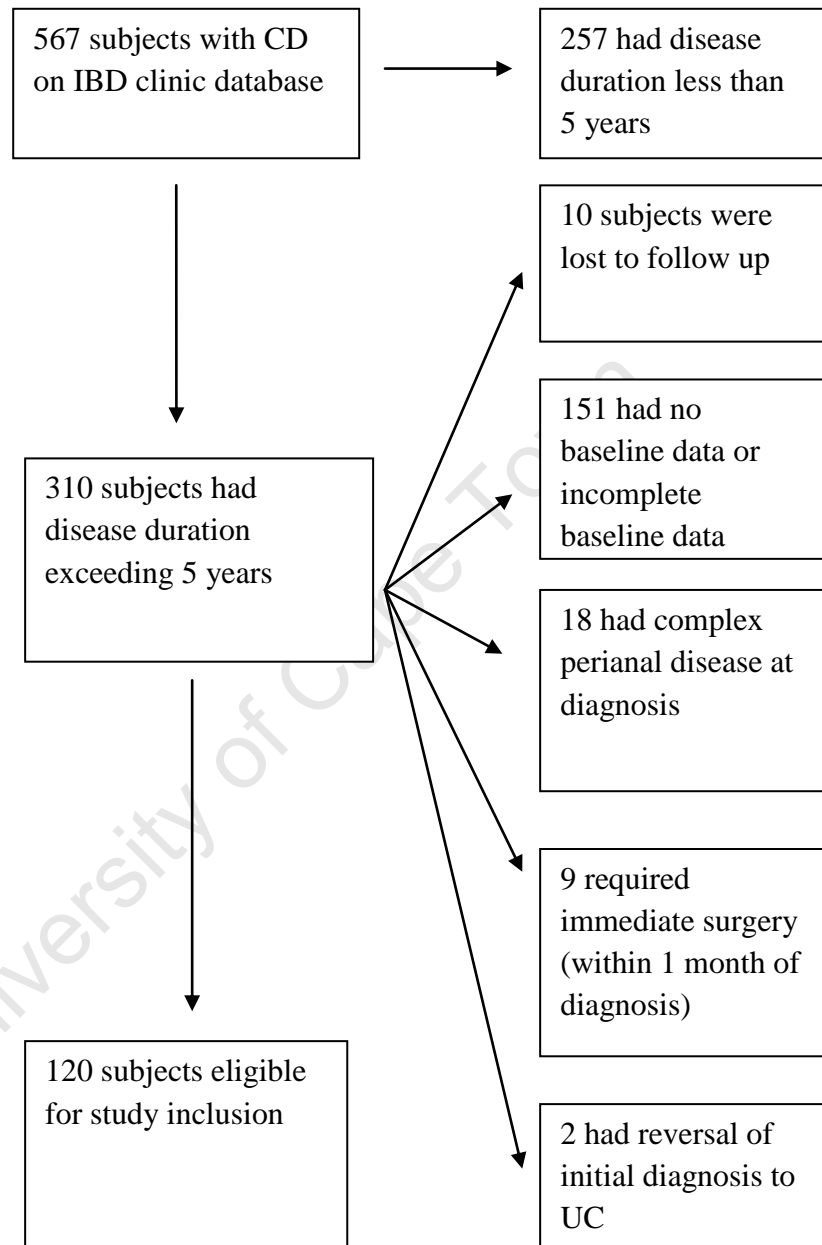
P[†] Perianal disease modifier

L4 can be added to locations L1–L3 to indicate coexisting upper GI disease.

†P can be added to any behaviour to indicate coexisting perianal disease.

Appendix 4

Study subject eligibility



Appendix 5: A summary of predictors of poor outcome CD

Outcome	Predictor	Reference
Severe CD	Significant weight loss at diagnosis	Loly <i>et al.</i> (2008)
	Stricturing CD (B2) at diagnosis	
Disabling CD	Age at diagnosis	Beaugerie <i>et al.</i> (2006)
	Corticosteroids for the first flare,	
	Perianal disease	
Disabling CD	Perianal disease at diagnosis	Loly <i>et al.</i> (2008)
	Corticosteroids to treat the first flare	
	Ileo-colonic location (L3)	
CD recurrence rates	Young age at diagnosis	Romberg-Camps <i>et al.</i> (2009)
	Current smoking	
Progression to complicated disease (B1 to B2 or B3)	Small bowel location, perianal disease	Tarrant <i>et al.</i> (2009)
	Genetic markers	Adler <i>et al.</i> (2011)
Surgery	Ileal location	Solberg <i>et al.</i> (2007);
	Serological markers	Romberg-Camps <i>et al.</i>
	Genetic markers	(2009)
	Granulomas	Dubinsky <i>et al.</i> (2008)
	Young age at diagnosis	Adler <i>et al.</i> (2011)
	Penetrating behaviour at diagnosis	Heresbach <i>et al.</i> (2005)
	Stricturing disease at diagnosis	Romberg-Camps <i>et al.</i>
	Smoking	(2009)
		Solberg <i>et al.</i> (2007)
		Romberg-Camps <i>et al.</i> (2009)
	Latakos <i>et al.</i> (2007)	
Colectomy	Deep colonic ulcers	Allez <i>et al.</i> (2002)