Predictive factors for an uncomplicated long-term course of Crohn's disease: A retrospective analysis

W. Kruis a,⁎, A. Katalinic b, T. Klugmann c, G.-R. Franke d, J. Weismüller e, L. Leifeld a, S. Ceplis-Kastner f, B. Reimers f, B. Bokemeyer g, h

a Evangelisches Krankenhaus Kalk, Innere Medizin, Köln, Germany
b Institut für Krebsepidemiologie, Universität Lübeck, Krebsregister Schleswig-Holstein, Lübeck, Germany
c Internistische Gemeinschaftspraxis, Leipzig, Germany
d Ärztehaus Südhang, Dinkelsbühl, Germany
e Gastroenterologische Gemeinschaftspraxis, Koblenz, Germany
f Ferring Arzneimittel GmbH, Kiel, Germany
g Gastroenterologische Gemeinschaftspraxis, Minden, Germany
h Department of General Internal Medicine I, Christian-Albrechts-University, University Hospital Schleswig-Holstein, Kiel, Germany

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Abstract

Background: Predictive factors for a mild course of Crohn’s disease (CD) may have therapeutic consequences, but as yet have not been identified.
Aims: To identify baseline factors that predict mild CD and design a predictive scoring system.
Methods: A retrospective, multicenter study of newly diagnosed CD patients allocated to mild CD (no therapy, mesalazine only, or mesalazine with a single initial short course of low-dose prednisone) or moderate CD (all other patients including resected patients).
Results: 162 patients (median follow-up 43 months) were analyzed: 47 mild CD and 115 moderate CD. For mild CD versus moderate CD, mean age at first diagnosis was higher (41.1 versus 33.9 years, p=0.02), mean C-reactive protein (CRP) concentration was lower (1.6 versus 3.6 mg/L, p<0.01), and perianal lesions were less frequent (0% versus 10.4%, p=0.02). The combined incidence of complications (stenosis, any type of fistula, extraintestinal complications or fever) was 21.3% in mild CD versus 35.7% in moderate CD (p=0.07). A scoring system based on age, CRP, endoscopic severity (adapted Rutgeert’s score), perianal lesions and combined incidence of complications was developed which can predict a mild prognosis at the initial diagnosis, giving patients the chance of simplified therapy and accelerated step-up in the event of treatment failure.

Abbreviations: CD, Crohn’s Disease; CDAI, Crohn’s Disease Activity Index; CRP, C-reactive protein; ECCO, European Crohn’s and Colitis Organisation; NPV, negative predictive value; PPV, positive predictive value; TNF-α, tumor necrosis factor alpha.

⁎ Corresponding author at: Evangelisches Krankenhaus Kalk, Buchforststrasse 2, D-51103 Köln-Kalk, Germany. Tel.: +49 221 8289 5289; fax: +49 221 8289 5291.
E-mail address: kruis@evkk.de (W. Kruis).

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1. Introduction

Crohn’s disease (CD) shows a highly variable clinical course. While up to a third of patients ultimately require surgery, 1–2, 10–25% experience no recurrence after the initial flare-up. 1–3 A significant proportion of CD patients requires only relatively mild treatment. In one population-based cohort, 57% of patients diagnosed with CD did not require corticosteroid therapy at any stage, 4 while in the recent IBSEN study 28% of patients remained steroid-free. 1 Even following referral to a specialist center, one study reported that corticosteroids were not necessary for 35% of first flare-up. 5 Many centers therefore adopt a ‘step-up’ approach to the management of CD, whereby less potent, safer therapies are initiated first, escalating treatment only in the event of non-responsiveness. Recent studies of ‘top-down’ versus ‘step-up’ therapy have shown conflicting results. A prospective randomized comparison between a step-up regimen with corticosteroids and a top-down strategy starting with infliximab showed favorable results for the top-down approach after six months, but significance was lost after 12 months. 6 A five-year prospective observational study concluded that indiscriminate use of biological therapy (‘top-down’ strategy) is not appropriate for moderate to severe CD. 7 Indeed, the recent European Crohn’s and Colitis Organisation (ECCO) management guidelines 8 point out that for selected patients with mild CD, one option is to start no active treatment. The guidelines also suggest that oral mesalazine can be used as first-line therapy for mildly active ileocaecal CD. 8 A single-center pilot study has reported that 18% of newly-diagnosed CD patients can be brought into remission and maintained successfully on mesalazine alone. 9

While a top-down approach may have prognostic benefits in selected patients, it exposes all patients to aggressive therapy with its associated risks and cost. Step-up treatment, the alternative strategy, can avoid these burdens in patients with mild disease. Intensification of treatment in patients who do not respond to first-line therapy enables the management of the course of CD to become more individualized. It would therefore be useful to predict at the time of diagnosis which patients are likely to have an uncomplicated course and are suitable candidates for mesalazine as first-line therapy. Predictive factors for relapse in CD have been extensively researched and proposed markers include young age, smoking, disease location and presence of stricturing disease, 2,5,10,11 increasing severity of mucosal lesions on endoscopy, 12 and laboratory values such as tumor necrosis factor alpha (TNF-α), 13 other cytokines 14,15 and C-reactive protein (CRP). 16 To date, however, potential predictive factors for a mild course of CD have not been evaluated.

Most treatment studies are performed in secondary or tertiary clinical settings. Such referral centers inevitably have a selected patient population that is unrepresentative of the general health care situation. Here, a retrospective study was undertaken to identify baseline factors that predict a mild course of disease in a sequential cohort of patients newly diagnosed with CD at gastroenterology outpatient centers in Germany and to design a scoring system able to predict a mild course of CD.

2. Methods

2.1. Study design

This was a retrospective study. All patients included in the analyses were referred to gastroenterology practices because of gastrointestinal symptoms, and were thus newly diagnosed cases. A total of 14 gastroenterology practices in Germany documented the initial diagnosis and undertook follow up during the period January 2007 to May 2010. The protocol and a patient informed consent form have been submitted for evaluation to a registered ethics committee, who had no legal or ethical concerns regarding the conduct of the study. Only data of patients who agreed to this data collection and source data verification by independent clinical monitors were captured.

2.2. Study recruitment

Private gastroenterology outpatient practices experienced in inflammatory bowel disease (IBD) management were chosen to participate if they agreed to the protocol, had sufficient experience with IBD and fulfilled the prerequisite of excellent documentation. In addition, all participating centers favored the concept of step-up treatment where possible, depending on disease severity. This concept included administration of mesalazine as a component of first-line treatment for newly diagnosed CD.

Ambulatory patients with a first diagnosis of CD established at the participating gastroenterology practice based on the guidelines of the German Gastroenterological Association (DGVS) 17 were included if they had been treated or observed for at least 12 months by the participating outpatient clinic. Patients who could not be treated as outpatients were excluded.

The proportion of patients who achieved remission and the time to remission was recorded, as well as the proportion of patients in whom step-up therapy was required and what type of therapy was required.

2.3. Data collection

Data were obtained from standard medical records by staff at each center and verified by external monitors. Data capture
was performed on paper Case Record Forms (CRFs). Source data verification was performed by the clinical monitors. Data were transferred and analyzed in a "pseudonymized" form.

Baseline data obtained at the time of first diagnosis included age, gender, ethnic origin, body weight/height, details of family history of IBD, smoker/non-smoker, and CRP level. The date and findings of first colonoscopy were recorded, including information on location (colon, ileum or upper gastrointestinal tract) and severity, based on an adapted version of Rutgeert's score (RS).\(^{18}\)

To ensure that endoscopic assessment was feasible in this retrospective study, and taking into account the simplicity of the RS in the assessment of the postoperative situation, we used an adapted Rutgeert's score (aRS) in the endoscopic assessment of the colon and the ileum. Compared to the original RS, the aRS differs in two regards. Firstly, the original score was designed for the postoperative situation while the aRS was used to assess the entire colon and terminal ileum in non-operated patients. Secondly, we amended the nomenclature and wording of the aRS in order to assess the colon, as follows: 0, no lesions (RS: 10, no lesions); 1, <5 aphthous lesions or ulcerations (RS: 11, <5 aphthous lesions); 2, >5 aphthous lesions or ulcerations with normal intervening mucosa (RS: 12, >5 aphthous lesions with normal mucosa between the lesions); 3, diffuse aphthous ileitis/colitis or ulcerations with diffusely inflamed mucosa (RS: 13, diffuse ileitis/colitis with diffusely inflamed mucosa); and 4, diffuse inflammation with larger ulcers and/or narrowing (RS: 14, diffuse inflammation, already with larger ulcers, nodules and/or narrowing). This adapted score has not previously been tested for validity and consistency in a prospective cohort.

Other data collected at the time of the initial diagnosis were endoscopic results (typical, matching CD, non-characteristically inflammatory or non-typical), histology (typical [i.e. epitheloid cell granuloma], matching CD, non-characteristically inflammatory or non-typical), the presence/absence and location of stenosis, penetration of the intestinal epithelium or fistulae, the presence/absence and type of perianal lesions or extra-intestinal manifestations and complications, presence/absence of fever (defined as > 38 °C). The combined incidence of one or more of the following was calculated: stenosis, any type of fistula, extraintestinal manifestations and fever. A diagnosis of CD required endoscopic and histologic proof of inflammation at two different time points or a very typical endoscopic and histologic picture on a single endoscopy, with exclusion of other inflammatory diseases.

The type of initial therapy and maintenance therapy was documented. The dose and duration of mesalazine treatment (if administered) were also recorded for both initial treatment and maintenance therapy. The use, type, and dates of step-up therapy were recorded. Surgery for CD during the observation period was also noted.

2.4. Statistical analysis

Patients fulfilling the inclusion criteria were divided retrospectively into two groups. Mild CD comprised patients who throughout follow-up received no other therapy than mesalazine, or mesalazine in combination with a single short (<12 week) course of low dose (≤40 mg/day) prednisone at the start of the treatment. Moderate CD comprised all other patients i.e. those who initially or throughout follow-up received medical treatment(s) or surgical intervention in addition to mesalazine or short-course, low-dose prednisone at the time of the first diagnosis. Patients who required bowel resection were assigned to moderate CD regardless of the type of medical therapy administered.

Selected baseline characteristics were compared between the two groups by univariate analysis (t-test, Chi square test) to identify factors predictive of a mild course of CD. All parameters which were significantly different between groups, or which showed a trend to significance (p<0.1) were included in a scoring system. Additionally, endoscopy (a prerequisite for the initial diagnosis) was considered to provide an objective measure of the structural status and was included in the scoring system. The accuracy of the scoring system for predicting a mild course of CD at the time of initial diagnosis was calculated based on sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) using different cut-off points.

3. Results

3.1. Study population and treatment

A total of 162 patients with a median follow-up observation time of 43 months were eligible for inclusion in the analyses. All patients were recruited from private-based outpatient practices. Of the 162 eligible patients, 47 (29.0%) met the criteria for inclusion in mild CD, while 115 patients (71.0%) met the criteria for inclusion in moderate CD. Demographic characteristics were similar between the two groups other than older age in mild CD (mean [SD] 41.1 [16.5] years versus 33.9 [14.5] years in moderate CD; p=0.02) (Table 1). The median (range) duration of follow-up was 45 (2–110) months in the mild CD cohort and 39 (11–109) months in the moderate CD cohort (n.s.).

Disease characteristics differed between the two groups (Table 1). The initial mean CRP concentration was significantly lower in mild CD (mean [SD] 1.6 [1.7] mg/L versus 3.6 [4.7] mg/L in moderate CD; p<0.01), while perianal lesions were observed only in moderate CD (p=0.02) (Table 1). Other disease characteristics demonstrated only slight differences such as slightly milder disease in colonic CD. Mucosal level histology and general endoscopic assessments were similar in both groups. Mucosal lesions (aRS score 2–4) occurred in 76.6% of patients in mild CD (36/47) and in 80.7% of patients in moderate CD (80.7%). The combined incidence of signs of severe or advanced CD such as stenosis, any type of fistula, extraintestinal manifestations or fever showed a trend towards a significant difference between groups (mild CD, 21.3%; moderate CD, 35.7%; p=0.07). Surprisingly, smoking status was similar in both groups.

Initial treatment on diagnosis and most intensive treatment administered during follow-up are summarized in Fig. 1. The majority of patients (approximately 78%) received either mesalazine only or mesalazine with short-course corticosteroids (Fig. 1). Almost 40% of patients ultimately required immuno-suppressive therapy.
3.2. Scoring system for the prediction of mild disease

A scoring system was developed based on age at first diagnosis, CRP concentration, endoscopic severity (aRS) and clinical severity as indicated by the presence/absence of perianal lesions and the combined incidence of stenosis, fistula, extraintestinal manifestations and fever (Table 2). Complete data for all five of these parameters were available in 104 patients (25 mild CD, 79 moderate CD), upon whom scoring calculations were based. Fig. 2 illustrates the distribution of scores in each group at the time of initial diagnosis, which prompted selection of scores 1, 2 and 3 as possible cut-off points for prediction of a mild disease course. As would be expected, the specificity of the scoring system increased and sensitivity decreased at higher cut-off points. PPV showed a more marked decline than NPV as the cut-off point increased (Fig. 3).

4. Discussion

In this cohort of CD patients, the course of the disease remained mild in 29% of patients over a median of ~3.5 years after first diagnosis. Although definitions vary, other studies have also consistently reported that a considerable proportion of patients with CD experience only a mild course of the disease. A prospective population-based IBSEN study of incident CD patients in Norway has previously reported that 28% of patients remained steroid-free for five years after initial diagnosis. Another population-based incident cohort study, undertaken in Germany, observed that only 34.7% patients required immunomodulation during the first...
25 months of the disease. A study from North America calculated that a representative patient spends 24% of the lifetime disease course in medical remission, 27% with mild disease, 1% with severe drug-responsive disease, 4% with severe drug-dependent disease, 1% in surgery and 41% in post-surgical remission. Probably the best characterized inception cohort, from a study undertaken in Copenhagen, reported the clinical course over a continuous five-year period (years 3–7 post-diagnosis). It found that in each year 25% of patients had active disease, 22% were in remission and 53% fluctuated between years of remission and relapse.

It could be argued that an observation period of five years may be too short to predict the life-long course of CD, and that the risk of structural damage may even increase in the later years of the disease. However, long-term observations have shown that the course of the disease is worse during the early years and that there is a tendency for inflammatory activity to burn out. We defined a mild disease course as requiring only treatment with aminosalicylates, with or without a short course of steroids. The Danish Crohn Colitis Database has previously reported that 31% patients were maintained only on aminosalicylates after one year, similar to our findings, while the Norwegian IBSEN study found that 54% of patients were receiving oral sulfasalazine and 5-aminosalicylic acid at five years after diagnosis. It appears that, in contrast to weak or negative recommendations from international guidelines, aminosalicylates are a preferred treatment for CD in routine practice.

In our analysis, we found younger age to be a convincing risk factor for a severe disease course. Other studies have also reported age of onset to be a prognostic factor, although with different thresholds for effect. Extensive investigations have also been carried out to determine the predictive capability of serum markers, most frequently CRP. Higher CRP levels during relapse are associated with a more severe clinical course and the IBSEN study found CRP levels to be a valuable predictive marker for CD over time. These, and findings from other studies, have led to the conclusion that CRP is useful as a laboratory marker for predicting prognosis and relapse in CD patients. We confirmed that high CRP levels at disease onset are prognostic for a poor disease course, while low CRP levels were associated with a more favorable prognosis.

Table 2  Scoring system to predict a mild course of CD at the time of initial diagnosis.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Presentation Points</th>
</tr>
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<tbody>
<tr>
<td>Age at first diagnosis, years</td>
<td>≤ 40: 1, &gt;40: 0</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>&lt;2: 0, 2 to &lt;4: 1, ≥4: 2</td>
</tr>
<tr>
<td>Endoscopic score</td>
<td>≤ 1: 0, &gt;1: 1</td>
</tr>
<tr>
<td>Perianal lesions</td>
<td>No: 0, Yes: 1</td>
</tr>
<tr>
<td>Complications: ≥1 of stenosis, any type of fistula, enterointestinal manifestations or fever &gt; 38 °C</td>
<td>No: 0, Yes (≥1): 1</td>
</tr>
</tbody>
</table>

CD, Crohn's disease and CRP, C-reactive protein.

Figure 1  Initial treatment at the time of diagnosis and most intensive medical treatment received during 48 months' follow-up in mild and moderate CD. Immunosuppressants comprised 6-mercaptopurine (6-MP) or methotrexate.

Figure 2  Scoring system results in mild CD and moderate CD at time of first diagnosis. See Table 2 for details of the scoring system.
Discussion of mucosal healing as a possible component in the staging of CD activity has drawn attention to a potential role for intestinal mucosa status as a prognostic marker. Although not statistically significant, we observed a tendency toward a milder disease course in patients with less severe findings on endoscopy at the onset of CD. This is compatible with other data in which mucosal healing after the first year predicted a more favorable course of CD thereafter.29 Similarly, a study from the Netherlands showed that initial treatment of active CD leading to mucosal healing resulted in a better five-year prognosis.30 These results led reviewers to conclude that the severity of endoscopic mucosal alterations and, conversely, mucosal healing are factors that influence the disease prognosis.9,31

Perianal lesions were only observed in the patients who experienced a more severe disease course in our population. Two other retrospective studies, from France and Belgium, also described the presence of perianal disease at the initial diagnosis of CD as a predictive factor for subsequent disabling disease.5,32

Extraintestinal complications, most often arthropathies, occur commonly in CD.33 Early studies in children described the need for more intense treatment such as steroid therapy or surgery in children with ileocolitis and extraintestinal complications,34 but further data on the prognostic significance of extraintestinal complications are lacking. In our population, extraintestinal manifestations occurred at a similar rate in patients with or without a mild disease course, but a wider category of complications including stenosis, fistula and fever as well as extraintestinal manifestations was significantly more frequent in patients with a moderate or severe disease course.

The rationale for introducing top-down treatment strategies following the advent of biologicals was to avoid disabling disease. Accordingly, attempts were made to define factors predictive for a more severe disease course but genetic, phenotypic and environmental factors for use in routine practice have not yet been identified and selection is instead largely based on clinical criteria.25 Considerable numbers of patients require only basic therapy with mesalazine, and overtreatment of these individuals using early biological therapy incurs risks such as serious side effects and economic waste. A prospective five-year study undertaken in a hospital referral center concluded that only 23% of patients with moderate or severe CD might have benefited from early biologic treatment.7

The scoring system presented here may be of value in identifying patients at the time of initial diagnosis who are likely to experience a mild disease course and in whom step-up treatment with early therapy escalation in the absence of an adequate response may avoid disabling disease while maximizing safety and minimizing cost.7 The scoring system may also be helpful to reevaluate the therapeutic efficacy of mesalazine in selected patients with CD. The scoring system aimed to identify patients with a prognosis of mild CD. In those patients a safe and simple treatment with mesalazine may achieve adequate efficacy. Since the intensity of therapy can escalate rapidly, an incorrect diagnosis of mild CD is relatively harmless, certainly compared to the risks associated with overtreatment in patients who truly do have mild CD. We propose that in the current scoring system, a score of ≤2 would seem to reflect sufficient sensitivity with acceptable specificity for the prediction of mild CD.

The main limitations of our study are the retrospective design and the relatively low number of patients. However, strict criteria applied during the screening process excluded many patients and avoided inclusion of weak data, and our findings are consistent with earlier published studies. The strict exclusion procedures, unfortunately, prevented analysis of higher numbers of eligible patients. Moreover, only 64% of patients provided a full data set upon which to base the development of the scoring system, which potentially limits its validity. However, those patients with a missing CRP value exhibited the same score distribution as the analyzed set (data not shown), which suggests that exclusion of so many patients may not have markedly affected the outcome. We are also aware that the presence of existing stenosis or fistulae can predict a more serious course of CD but definition of severity is challenging and in order to provide a simple and practical scoring system we have not included these parameters. Future prospective studies could more accurately define severity of stenosis and fistulae, and assess the merit of their inclusion as predictive factors.

Lastly, genome-wide association studies have shown that CRP promoter polymorphisms influence circulating CRP levels such that in patients with genetically determined CRP(−), CRP cannot be used as a marker of inflammation. This may explain the limited sensitivity of CRP as a biomarker for inflammatory activity of IBD. To our knowledge, there is a lack of representative epidemiological data on CRP-associated genetic malfunction in patients with IBD. We consider that this lack of diagnostic accuracy can, to some extent, be overcome by combined scores. Despite these issues, however, our study is the first to propose a scoring system for the prediction of mild CD and we believe that the quality of the current data is able to generate a valuable hypothesis to be validated in further prospective studies. Such studies could expand the criteria for disease progression from solely clinical and endoscopic indices to include patient perceptions of disease severity using appropriate quality of life instruments.

In conclusion, a considerable number of patients with CD experience only a mild course of the disease and require only basic therapy. Older age, lower CRP, absence of perianal disease or extraintestinal complications and milder endoscopic
alterations at the initial diagnosis are predictive of a mild disease course. On the basis of a scoring system predictive for mild CD, simple therapy with mesalazine could be started and thus avoid the risk of overtreatment while preserving the opportunity for accelerated step-up therapy in patients with more severe disease.

**Conflicts of interest**

WK has received honoraria for lecturing and consultation from Falk Merckle-Recordati, Abbott, Shire, Ferring Arzneimittel GmbH, UCB, Otsuka, Nikkiso; AK has received consultancy honoraria from Ferring Arzneimittel GmbH; and BB has received consultancy honoraria from Abbott, MSD, Shire, Ferring, UCB, Movetis, Vifor and Medice, and speakers honoraria from Abbott, Ferring Arzneimittel GmbH, MSD, Merckle, Falk, HLR and UCB. LL has received speakers honoraria from Falk Foundation. SC-K and BR are employees of Ferring Arzneimittel GmbH, Kiel, Germany. TK, G-RF and JW have no conflicts to declare.

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**Author contributions**

WK participated in the design of the study, analysis of the results, and preparation of the manuscript. AK provided biostatistical support. BB participated in design of the study and creation of the study protocol, patient enrolment, analysis of the results and preparation of the manuscript. TK, G-RF, JW and LL undertook patient enrolment and data collection. SC-K and BR participated in the design of the study and analysis of the results.

**References**


