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CRP Correlates with Clinical Score in Ulcerative Colitis but Not in Crohn's Disease

Alexander D. Rodgers · Adrian G. Cummins

Abstract The aim of this study was to prospectively evaluate the correlation between clinical scoring systems and C-reactive protein (CRP) in inflammatory bowel disease. The modified Harvey-Bradshaw index was used in 40 patients (58 assessments) with Crohn's disease, and the Lichtiger score in 29 patients (36 assessments) with ulcerative colitis. In ulcerative colitis, CRP was elevated in 14%, 42%, 64%, and 83%, respectively, of subjects with quiescent, mild, moderate, and severe disease. There was a linear correlation of log(CRP) with clinical score except for proctitis. In Crohn's disease, CRP was elevated in 54%, 70%, 75%, and 100%, respectively, of subjects with quiescent, mild, moderate, and severe disease. We conclude that the clinical score has a good correlation with CRP in ulcerative colitis except for proctitis, whereas clinical score has a poor correlation with CRP in Crohn's disease, particularly in those with clinically quiescent, fibrostenotic, and ileal disease.

Keywords C-reactive protein · Crohn's disease · Erythrocyte sedimentation rate · Inflammatory bowel disease · Ulcerative colitis

Introduction

Ulcerative colitis (UC) and Crohn's disease (CD) are inflammatory bowel disorders characterized by a fluctuating disease course with episodes of inflammation causing clinical disease which generally respond to anti-inflammatory treatment such as corticosteroid or immunosuppression. Various methods are used for assessing the activity of inflammatory bowel disease. Direct visualization of colonic or ileal mucosa with colonoscopy and histological assessment of mucosal biopsy specimens are regarded as the gold standard for the assessment of disease activity and extent [1–3]. The presence of active disease is easier to determine in UC, as the disease commences distally in the rectum and can be visualized at sigmoidoscopy. Documenting active disease in CD is more difficult because of its variable location and patchy involvement along the gastrointestinal tract.

Clinical disease activity scores and laboratory tests (in particular, the inflammatory markers of erythrocyte sedimentation rate [ESR] and C-reactive protein [CRP]) are measures that are used to determine the severity of inflammatory bowel disease. The subjective nature of clinical scoring symptoms makes them prone to bias from noninflammatory bowel conditions. This includes patients with CD in whom symptoms may be a result of bile salt diarrhea, small bowel bacterial overgrowth, or fibrotic strictures in the absence of inflammation [4]. The coexistence of idiopathic or post-inflammatory irritable bowel syndrome is also common. Inflammatory markers are limited by their lack of specificity to inflammation within the gut.

There have been conflicting reports on the ability of ESR and CRP to predict disease activity in UC, but several studies have shown that site of disease has a major impact, with inflammation limited to rectum or sigmoid colon having low ESR and CRP despite severe disease [5, 6]. In CD, ESR correlates well with disease limited to the colon but not that in the small bowel [5, 7, 8]. CRP correlates well with disease activity in CD [5, 9].

Various studies have looked at the accuracy of both clinical scoring systems and inflammatory markers at assessing activity of inflammatory bowel disease, but few have directly

A. D. Rodgers · A. G. Cummins (✉)
Department of Gastroenterology and Hepatology,
The Queen Elizabeth Hospital, Woodville Road,
Woodville South, South Australia 5011, Australia
e-mail: adrian.cummins@nwahs.sa.gov.au

compared these two methods. The aim of this study was to evaluate prospectively the correlation between simple subjective clinical scoring indices and laboratory markers of inflammation in the assessment of patients with inflammatory bowel disease. The effects of disease extent in UC and disease phenotype and location in CD on the correlation were also assessed. The role of hemoglobin (Hb) and plasma albumin levels in predicting disease activity and severity was also measured.

Subjects and methods

Subjects

Patients with known or newly diagnosed inflammatory bowel disease who presented to The Queen Elizabeth Hospital between March 2002 and January 2004 were enrolled in this study. Patients were inpatients, outpatients, or those presenting for an endoscopic procedure. Patients were excluded if they had concurrent illness likely to cause raised levels of inflammatory markers. Fifty-eight assessments were made in 40 patients with CD, and 36 assessments in 29 patients with UC.

In the UC group, 17 assessments were made in females and 19 in males. The mean (range) age was 59.1 (24–79) years. Eight cases had a new diagnosis of UC. Of the other 28 cases, 24 were on corticosteroid, sulfasalazine, and/or immunosuppression. In the CD group, 25 of the assessments were made on females, and 33 on males. The mean (range) age was 42.4 (17–72) years. CD was newly diagnosed in four cases. Forty-five of the cases were on therapy; 35 of these were on an immunosuppressive. Twenty-four cases had had previous surgery (bowel resection, abscess drainage, or fistulotomy) for their CD.

Assessment

The clinical activity score was assessed in UC using the Lichtiger score [10]. Patients with CD had their activity score measured using the modified Harvey-Bradshaw index [11]. UC was defined as quiescent when the Lichtiger score was 0–1, mild severity when 2–8, moderate when 9–14, and severe disease when 15–21. CD was defined as quiescent when the Harvey-Bradshaw score was 0–3, mild severity when 4–7, moderate when 8–11, and severe disease when ≥ 12. This division of activity corresponds approximately to CDAI scores of 150, 250, and 350, respectively. Blood tests were performed on all patients with measurements of ESR, CRP, complete blood examination (CBE), and plasma albumin concentration. A raised ESR was defined by the following equations using the Westergreen method, i.e., for men, age (years)/2 and, for women, (age + 10 years)/2. CRP

was defined as elevated at a level > 10 mg/L. Hb and plasma albumin were measured as grams per liter.

Flexible sigmoidoscopy or colonoscopy was performed in 33 of the 36 UC cases. The three cases without investigation either showed no evidence of active disease based on Lichtiger score and inflammatory markers or refused further investigation. If there was macroscopic evidence of active colitis, this was confirmed by biopsy. The extent of inflammation was not defined in six of those undergoing an endoscopic procedure. Colonoscopy, small bowel follow-through, labeled white cell scan, or laparotomy was performed in 41 of the 58 cases of CD. Fistulas were present in six additional cases, providing evidence of active disease. In the remaining 11 cases, no investigation was performed either because there was no evidence of active disease on clinical score or on inflammatory markers or because the patient declined investigation.

Ethics

This study was approved by the Human Ethics Committee of The Queen Elizabeth Health Service. Each subject gave informed consent and patient anonymity was preserved. The study conformed to the Declaration of Helsinki as revised in Edinburgh, 2000.

Statistical analysis

Statistical analysis was performed by Ms. Janine Jones of BiometricsSA (South Australia). An analysis of variance was performed to determine the mean subjective score in each of the four disease severity subgroups in both UC and CD. A polynomial contrast was performed to test for a linear trend among the four ordered subjective groups and each of the objective scores using an *F*-test.

Results

Ulcerative colitis

Subjects were divided into quiescent, mild, moderate, and severe groups based on their Lichtiger clinical score and compared with ESR, CRP, Hb, and plasma albumin levels (Table 1). The ESR was increased in 29%, 25%, 73%, and 100%, and CRP was elevated in 14%, 42%, 64%, and 83%, respectively, of subjects with quiescent, mild, moderate, and severe disease. There was a positive linear correlation of ESR and log(CRP) with clinical score except for proctitis. There was a negative linear correlation for clinical score and plasma albumin. Five of the seven subjects with quiescent disease had either sigmoidoscopy or colonoscopy and two of these five had proctitis (one) or left-sided disease (one) with

Table 1 Comparison of disease activity based on clinical Lichtiger score and ESR, Hb, and albumin in UC

Clinical severity of disease	Mean ESR (% elevated)	Mean CRP (% elevated)	Mean Hb, male/female (% low)	Mean albumin (% low)
Quiescent ($n = 7$)	25 (29)	7.8 (14)	144/123 (14)	40 (14)
Mild ($n = 12$)	22 (25)	19 (42)	151/117 (8.3)	42 (8.3)
Moderate ($n = 11$)	48 (73)	57 (64)	127/122 (27)	37 (36)
Severe ($n = 6$)	56 (100)	79 (83)	143/109 (33)	36 (33)
Linear P	0.008	0.002 (log CRP)	0.062 (male) 0.45 (female)	0.036

no rise in inflammatory markers. Eleven of 12 subjects with mild active disease had sigmoidoscopy or colonoscopy and 10 showed evidence of active disease endoscopically. Five subjects had evidence of colitis and normal inflammatory markers. All six cases with severe disease clinically had raised ESR and five subjects had raised CRP (83%). All had active colitis confirmed endoscopically extending at least as far as 50 cm proximally. Two of these cases required semi-urgent total colectomy. Significant linear trends were found between the mean level of the Lichtiger score in the different disease severity subgroups and the ESR ($P = 0.008$) and log(CRP) ($P = 0.002$). There was no relationship between the extent of disease activity on the Lichtiger score and ESR, CRP, Hb, and plasma albumin (Table 2). Extent of disease, however, was not available in eight subjects.

Crohn's disease

Subjects were divided into quiescent, mild, moderate, and severe groups based on their Harvey-Bradshaw clinical score and compared with ESR, CRP, Hb, and plasma albumin levels (Table 3). ESR was raised in 61%, 79%, 75%, and 100%, and CRP was elevated in 54%, 70%, 75%, and 100%, respectively, of subjects with quiescent, mild, moderate, and severe disease. There was no significant correlation of ESR and CRP with clinical score. Six of seven patients with quiescent disease who were investigated by sigmoidoscopy or colonoscopy had active disease with raised inflammatory markers. Thus, the Harvey-Bradshaw clinical score considerably underestimated activity of CD. Sixteen patients investigated endoscopically with mild disease all had raised inflammatory markers and active disease. Two cases with

severe disease had raised ESR and CRP. One case had ileocolitis and the other ileitis. There was no significant correlation of a linear trend between the Harvey-Bradshaw score and the ESR and CRP. The site of disease (colonic, ileocolonic, or ileal) did not correlate with ESR, CRP, Hb, or albumin except for fall in Hb in males and rectosigmoid disease (Table 4). In 20 cases, there either was no evidence of active disease or the location of disease was not determined. Subjects with CD were divided into one of three phenotypes based on the predominant feature of their disease: inflammatory disease, fistulizing disease, and fibrostenotic disease. Inflammatory disease was present in 78%, fistulizing disease in 13%, and fibrostenotic disease in 17% of subjects. The effect of these different phenotypes on the modified Harvey-Bradshaw score and on the objective measures was assessed (Table 5). The only correlation of phenotype was a fall in Hb. In 13 cases, either there was no evidence of active disease or the phenotype could not be categorized.

Discussion

Our study found that there was a significant correlation between clinical score and inflammatory markers in subjects with UC but not in subjects with CD. The correlation in UC was lost in distal disease and proctitis, i.e., it has to extend beyond the sigmoid colon. In CD, the clinical score underestimated the endoscopic assessment even in quiescent disease.

Previous studies have made conflicting reports on the ability of ESR to predict disease activity in UC. Some studies have reported a good correlation [12, 13], while others have

Table 2 Effect of disease extent on Lichtiger score, ESR, CRP, Hb, and plasma albumin in UC

Extent of disease	Mean Lichtiger score	Mean ESR (% elevated)	Mean CRP (% elevated)	Mean Hb, male/female (% low)	Mean albumin (% low)
No active disease ($n = 4$)	2	16 (25)	9 (25)	147/125 (0)	40 (0)
Proctitis ($n = 3$)	4.7	13 (0)	4 (0)	145/132 (0)	45 (0)
Limited to rectosigmoid ($n = 10$)	7.8	22 (40)	11 (20)	141/129 (30)	41 (10)
Extending beyond rectosigmoid ($n = 11$)	11.7	50 (82)	71 (100)	145/114 (18)	35 (45)

Table 3 Comparison of disease activity based on Harvey-Bradshaw index, ESR, CRP, Hb, and plasma albumin in CD

Clinical severity of disease	Mean ESR (% elevated)	Mean CRP (% elevated)	Mean Hb, male/female (% low)	Mean albumin (% low)
Quiescent ($n = 13$)	38 (61)	21 (54)	139/127 (15)	43 (0)
Mild ($n = 28$)	54 (79)	44 (70)	122/124 (50)	37 (18)
Moderate ($n = 15$)	51 (75)	45 (75)	139/113 (40)	36 (15)
Severe ($n = 2$)	70 (100)	94 (100)	113/94 (100)	36 (0)
Linear P	0.192	0.118	0.216 (male) 0.031 (female)	0.035

shown no correlation between ESR and disease activity assessed clinically [7, 13] or endoscopically [14]. We found a significant linear trend between the mean Lichtiger score and the ESR and CRP in the different disease severity subgroups. The mean ESR in quiescent, mild, moderate, and severe disease was 25, 22, 48, and 56, respectively, and that for CRP was 8, 19, 57, and 79, respectively. A previous study has shown that the level of ESR was associated with the extent of disease except in the rectum and distal sigmoid colon [5]. Similar findings have been reported for CRP [6]. We found that ESR and CRP were normal in proctitis. The mean ESR was 22 and the CRP was 11 for disease limited to the sigmoid colon. As disease extended beyond the sigmoid, the mean ESR increased to 50 and the CRP to 71. The mean Lichtiger score similarly increased with extent of disease.

Previous studies have shown that CRP correlates well with disease activity in CD, including the CDAI, colonoscopic appearance, and extent of disease [7, 9–11, 15]. We found, however, that the linear trend between the mean modified Harvey-Bradshaw score and the levels of ESR and CRP in the different disease severity subgroups was not statistically significant. The mean ESR was 38, 54, 51, and 70 and the mean CRP was 21, 44, 45, and 94 for quiescent, mild, moderate and severe disease, respectively. Six of thirteen cases (46%) with quiescent disease had radiological or colonoscopic evidence of active disease, 61% had elevated ESR, and 54% had raised CRP. This indicates that lack of symptoms in CD does not necessarily imply absence of inflammation. In contrast, a recent study by Chamouard et al. [19] found that the value of CRP was reasonably correlated with activity of clinical scores of CDAI or van Hees index, but their study included two patients with extremely active disease (e.g., CDAI of 600–700), which is just not seen in our clinical practice. It is unclear whether their study was

prospective. Our experience is that patients present earlier or are treated before this degree of activity occurs. These extreme endpoints could improve considerably the correlation between CRP and clinical scores of activity, but data from the in-between range are not as useful in correlating CRP and clinical score in the majority of patients.

Studies have found a better correlation with ESR and clinical activity in CD in colonic rather than small bowel disease, in which a negative association has been reported [5, 7, 8]. Our data agree with these findings, with a higher mean ESR of 69 in colonic disease, versus 44 in ileal disease. A previous study found no difference in CRP concentration between small and large bowel disease [11]. We found that 94% of those with colonic disease had raised CRP, with a mean of 69, compared to 64% of those with ileal disease, with a mean value of 32. This indicates that both CRP and ESR are more sensitive to colonic than ileal inflammation. A recent study of Crohn's subjects with low CRP also found predominantly ileal disease even with clinically active disease [16]. In contrast, another study found that CRP was associated with clinical activity as well as endoscopic inflammation but not radiologic activity [17]. Vermeire and co-authors have reviewed laboratory markers and IBD, and concluded that ESR and CRP were useful but noted heterogeneity in response [18].

The correlation between clinical score and inflammatory markers was weaker when considering the specific site of disease. Those with ileal disease had a higher Harvey-Bradshaw score, with a mean value of 9.5, than those with colonic disease, who had a mean value of 5.9 but lower inflammatory markers. Those with ileocolonic disease had a mean Harvey-Bradshaw score of 7.2, with inflammatory markers similar to those with ileal disease. Inflammatory markers were elevated in a high percentage of cases with

Table 4 Effect of site of disease on Harvey-Bradshaw score, ESR, CRP, Hb, and albumin in CD

Disease location	HBS	ESR mean (% elevated)	Mean CRP (% elevated)	Mean Hb, male/female (% low)	Mean albumin (% low)
Colonic ($n = 18$)	5.9	69 (100)	69 (94)	129/121 (33)	37 (28)
Ileocolonic ($n = 6$)	7.2	39 (67)	41 (67)	151/136 (0)	41 (0)
Ileal ($n = 14$)	9.5	44 (71)	31.5 (64)	125/121 (64)	38 (21)

Table 5 Effect of disease phenotype on Harvey-Bradshaw score, ESR, CRP, Hb, and albumin in CD

Phenotype	HBS	Mean ESR (% elevated)	Mean CRP (% elevated)	Mean Hb, male/female	Mean albumin (% low)
Inflammatory ($n = 35$)	6.7	59.3 (91)	55 (86)	136/128 (40)	38 (17)
Fistulizing ($n = 7$)	7.4	78.6 (100)	31 (86)	110/103 (86)	38 (0)
Stenotic ($n = 3$)	7.3	7.3 (0)	2.6 (0)	128/138 (33)	36 (67)

inflammatory or fistulizing disease. Those with stenotic disease, however, had a high clinical score in the absence of markers of inflammation.

CRP has been shown to be a more sensitive marker of disease activity than ESR, particularly in CD [6]. We found that in both UC and CD subjects, the percentage of patients with raised ESR and CRP and their mean levels were comparable for each stage of clinical disease severity and for disease location. In cases with fistulizing CD, the ESR was elevated to higher levels than the CRP (means of 78.6 and 31, respectively).

Hb was generally a nonspecific marker of disease activity in CD and an insensitive marker of activity in UC. Anemia was common in CD patients, including 50% of these with clinically mild disease and 100% with severe disease. A significant trend, however, was detected between the mean levels of Hb for females (but not males) and the mean Harvey-Bradshaw score. A high proportion of patients with fistulizing and ileal CD were anemic (86% and 64% respectively) compared with other phenotypes. In UC, one-third of patients with severe disease were anemic, compared with 8.3% of patients with mild disease, with the mean Hb falling from 151 to 143 in males and 117 to 109 in females. The trend was not statistically significant.

Plasma albumin was low in a higher proportion of UC patients who had moderate or severe disease (36% and 33% respectively) than in those with mild disease (8.3%). A smaller proportion of patients with CD had low albumin than of those with UC (18% with mild disease, 15% with moderate disease, and none with severe disease). A statistically significant association was demonstrated between subjective scores and plasma albumin in both UC and CD.

In conclusion, ESR and CRP generally have a good correlation with clinical activity scores in UC. Patients with distal UC were an exception, particularly those with only proctitis, which agrees with previous studies [5, 6]. We found a poor correlation in CD, particularly in those with fibrostenotic disease, ileal disease, and clinically quiescent disease, in which the majority of cases had raised inflammatory markers. In addition, a linear trend in CD was not evident due to elevated ESR and CRP even in quiescent and mild disease, indicating continuing inflammation in the absence of symptoms. In CD patients, we also found that both ESR and CRP were more sensitive to colonic rather than ileal or ileocolonic disease.

Clinicians in practice rely on a combination of history, physical examination findings, and investigations to determine the presence of active disease. A better understanding of the correlation between subjective measures and objective scores (in particular inflammatory markers) will help clinicians in their assessment of patients with inflammatory bowel disease.

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