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Usefulness of C-Reactive Protein as a Disease Activity Marker in Crohn's Disease according to the Location of Disease

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Background/Aims: C-reactive protein (CRP) is a serologic activity marker in Crohn's disease (CD), but it may be less useful in evaluating CD activity in ileal CD patients. We aimed to investigate the usefulness of CRP as a disease activity marker in CD according to disease location. **Methods:** Korean CD patients in a single hospital were evaluated. Factors associated with elevated CRP concentration at the time of diagnosis of CD and the association between the physician's prediction regarding upcoming surgery and the sites of the lesions directly related to surgery were analyzed. **Results:** Of 435 CD patients, 25.7%, 6.9%, and 67.4% had ileal, colonic, and ileocolonic CD, respectively. Multivariate analysis revealed that an elevated erythrocyte sedimentation rate, reduced serum albumin, CD activity index (CDAI) >220, and ileocolonic/colonic location were associated with an elevated CRP level and that the CRP level was significantly correlated with the CDAI in all CD patients (γ=0.466, p<0.01). However, the correlation coefficient was dependent on the location, with values of 0.395, 0.456, and 0.527 in patients with an ileal, ileocolonic, and colonic disease location, respectively. Surgery for ileal lesions was less predictable than surgery for ileocolonic or colonic lesions during follow-up. **Conclusions:** CRP is less useful as a disease activity marker in patients with ileal CD than those with ileocolonic or colonic CD. **(Gut Liver 2015;9:80-86)**

Key Words: Crohn disease; C-reactive protein; Inflammation

INTRODUCTION

C-reactive protein (CRP) is a marker of inflammation, and serum CRP concentration reflects disease activity in patients with Crohn's disease (CD).[1,2] Although CRP concentration shows significant correlations with other disease activity markers of CD, including the Crohn's disease activity index (CDAI), simplified endoscopic score of CD (SES-CD), and concentrations of interleukin (IL)-6, fecal calprotectin, and fecal lactoferrin,[3-5] this correlation seems to be less significant in patients with ileal CD than in those with ileocolonic and colonic CD. A study evaluating the relationships between CRP concentration and clinical, endoscopic, histologic, and radiographic activity in CD patients suggested that abnormal small bowel on radiographic images was not significantly associated with CRP elevation.[2] A prospective evaluation of 223 patients with clinically active CD, 22 with persistently low (<1 mg/dL) serum CRP concentrations and 201 with high serum CRP concentrations, found that the low CRP group was characterized by almost exclusive ileal distribution (95%).[6] These studies, however, did not evaluate whether the poor correlation between serum CRP and disease activity in patients with ileal CD would influence clinical management.

We therefore analyzed our hospital-based database of Korean CD patients to determine whether the clinical usefulness of serum CRP is dependent on lesion location.

MATERIALS AND METHODS

1. Patients

From June 1989 to January 2011, a total of 1,748 CD patients were registered in the database of the Inflammatory Bowel Disease (IBD) Clinic of Asan Medical Center. Our diagnostic criteria of CD were described previously.[7-9] To eliminate the possible influence of treatment for CD on serum CRP concentration, we

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excluded 1,289 patients who were referred to our clinic after starting treatment for CD in other hospitals. We also excluded patients with an uncertain diagnosis (n=2), those who did not undergo sufficient work-up for CD (n=1), those for whom initial serum CRP concentrations were unavailable (n=20), and those with concomitant bacterial infection at the time of diagnosis (n=1). This study therefore included 435 CD patients who were first diagnosed with or first treated for CD at our institution (Fig. 1). The Institutional Review Board of Asan Medical Center approved this study.

2. Methods

All medical records, including laboratory data, endoscopic findings, and radiologic studies, were reviewed. The patients were categorized by age at diagnosis (A1 ≤16 years, A2 17 to 40 years, and A3 >40 years), disease location (L1 ileum, L2 colon, and L3 ileocolon) and disease behavior (B1 inflammatory, B2 stricturing, and B3 penetrating) according to the Montreal classification.[10] We evaluated the correlation between CDAI and other serologic markers at diagnosis, including CRP and serum albumin concentrations, erythrocyte sedimentation rate (ESR), platelet count, and white blood cell (WBC) count, according to disease location. CRP concentration higher than 0.6 mg/dL was regarded as elevated CRP. All laboratory tests were performed at the time of diagnosis or before starting treatment for CD.

Of the 435 included CD patients, 96 patients underwent 112 bowel resection operations from June 1989 to April 2011. Thirty-eight of these operations were excluded from analysis, including surgery performed for diagnostic purposes, surgery performed at referring hospitals before diagnosis of CD, insufficient preoperative data including CRP concentration, surgery related to postoperative enterocutaneous fistula, and surgery unrelated to CD. The remaining 74 operations were included in this analysis. The indication, main site of lesions directly related to surgery, the date of surgery predicted by the physician, and the maximal preoperative serum CRP concentration (measured between 6 months and 2 weeks before surgery) were reviewed (Fig. 2). 'Predicted' surgery was defined as an operation per-

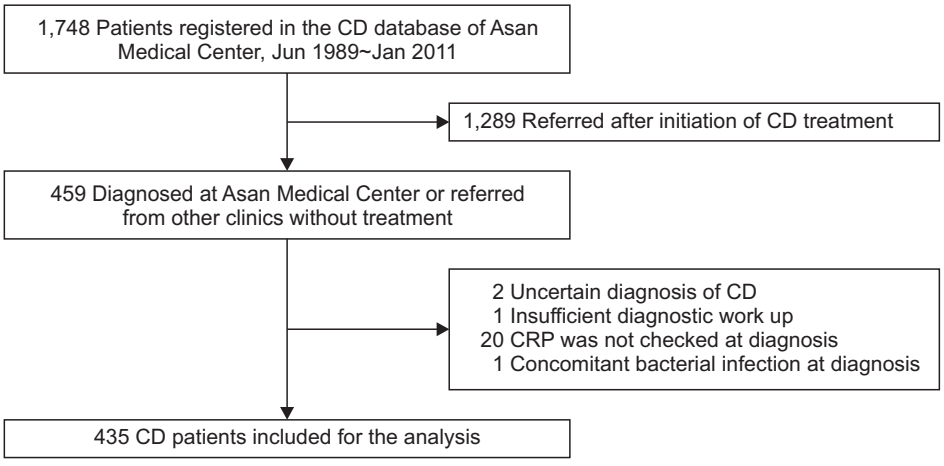

Fig. 1. Data extraction process for analyzing factors associated with an elevated C-reactive protein (CRP) at the time of Crohn's disease (CD) diagnosis.

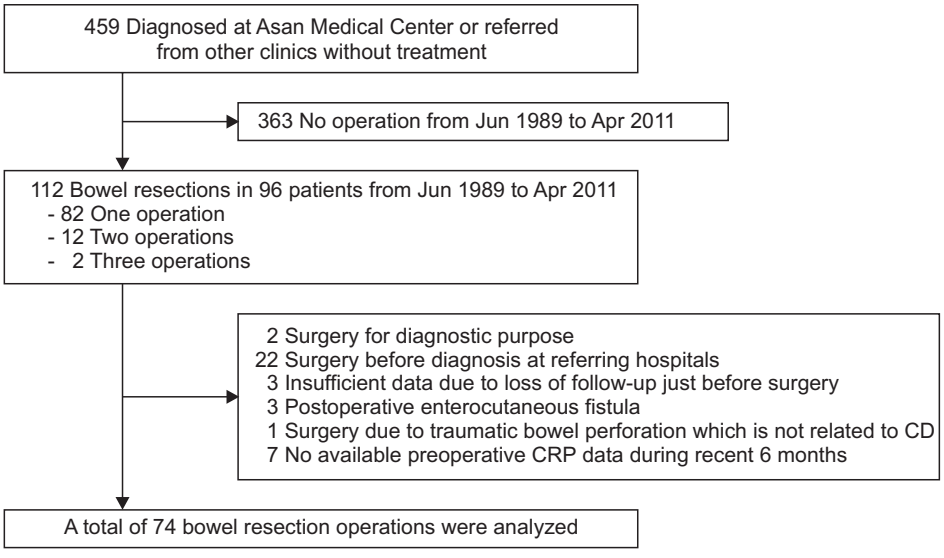

Fig. 2. Data extraction process for analyzing the predictability of surgery in Crohn's disease (CD) patients during follow-up.
CRP, C-reactive protein.

formed after a physician's recommendation or consultation with a surgeon at least 2 weeks before the operation date, based on clinical findings including symptoms, signs, laboratory results, and/or radiologic findings.

3. Statistical analysis

Univariate analyses of the associations between serum CRP concentrations and inflammatory markers, disease activity markers, and clinical parameters, such as CD location and behavior, were determined using chi-square tests, and a logistic regression model was used for multivariate analysis. Because of the skewed distribution of serum CRP concentrations, Pearson correlation coefficient was utilized to assess the correlation between log-transformed CRP concentration and CDAI at the time of diagnosis. Measurable parameters in two groups were compared using Student t-tests. All statistical analyses were performed using SPSS for Windows version 18.0 (SPSS Inc., Chicago, IL, USA) and a p-value <0.05 was regarded as statistically significant.

RESULTS

1. Baseline characteristics of the patients

The median age at diagnosis was 24.7 years (range, 12.5 to 74.5 years), and the male-to-female ratio was 2.7 to 1. According to the Montreal classification, ileocolonic location and inflammatory behavior were the most common features at the time of diagnosis of these Korean CD patients (Table 1). Mean CRP concentration at diagnosis or before starting treatment of CD was significantly lower in ileal CD (2.0±2.5 mg/dL) than in ileocolonic (3.9±3.8 mg/dL) or colonic (4.8±4.2 mg/dL) CD (p<0.001). Elevated CRP concentration at diagnosis was less common in ileal CD (55.3%) than in ileocolonic (85.7%) or colonic (90.0%) CD (p<0.001).

2. Association between serum CRP at diagnosis and various parameters: univariate

Of the 435 patients, 95 had normal CRP concentrations and 340 had elevated CRP concentrations at the time of diagnosis. Univariate analysis showed that elevated CRP at diagnosis was significantly correlated with mild/moderate/severe CDAI, elevated WBC count (>10,000/mm^3), elevated platelet count (>350,000/mm^3), decreased serum albumin level (<3.3 g/dL), elevated ESR (≥20 mm/hr), ileocolonic or colonic location, and presence of active perianal fistula at diagnosis. By contrast, elevated CRP level was not associated with the presence of upper gastrointestinal modifier and the behavior of CD at diagnosis (Table 2).

In the ileal CD subgroup, abnormal platelet count (p=0.002), decreased serum albumin level (p<0.001), elevated ESR (p<0.001), and moderate to severe CDAI were significantly associated with elevated CRP level at diagnosis, but abnormal WBC count was not.

According to the multivariate analysis, elevated ESR, decreased serum albumin level, and CDAI >150 were significantly associated with elevated CRP level at diagnosis in the patients with ileocolonic/colonic CD (Table 3). Elevated ESR and decreased serum albumin level at diagnosis were also independently associated with elevated CRP level in the ileal CD group, whereas CDAI at diagnosis was not (Table 3).

3. Location dependence of the correlation between serum CRP level and CDAI at diagnosis

Serum CRP concentration and CDAI at diagnosis were significantly correlated, with a Pearson correlation coefficient (γ) of 0.466 (p<0.01). In subgroup analysis according to the location of disease, Pearson correlation coefficients in patients with ileal, ileocolonic, and colonic CD were 0.395, 0.456, and 0.527, respectively (p<0.01 for all subgroups). Despite the lack of statistically significant differences, there was a clear trend toward weaker correlation between serum CRP concentration and CDAI at diagnosis in ileal CD than in colonic CD.

4. Physician's prediction of upcoming surgery, preoperative serum CRP, and lesion sites related to surgery

The main sites of the lesions directly related to surgery were

Table 1. Baseline Characteristics of 435 Korean Patients with Crohn's Disease First Diagnosed or Treated at Asan Medical Center

Clinical parameter	No. (%)
Gender	
Male	318 (73.1)
Female	117 (26.9)
Age group at diagnosis, yr	
<16 (A1)	49 (11.3)
17–40 (A2)	347 (79.8)
>40 (A3)	39 (9.0)
Smoking status at diagnosis	
Never smoker	277 (63.7)
Ex-smoker	26 (6.0)
Current smoker	126 (29.0)
Unknown	6 (1.4)
Disease location at diagnosis	
Ileal (L1)	112 (25.7)
Colonic (L2)	30 (6.9)
Ileocolonic (L3)	293 (67.4)
Disease behavior at diagnosis	
Inflammatory (B1)	326 (74.9)
Stricturing (B2)	59 (13.6)
Penetrating (B3)	50 (11.5)
Perianal fistula at diagnosis	
None or healed	376 (81.9)
Active	83 (18.1)

categorized as the ileum, ileocolon, and colon by analyzing preoperative endoscopic and radiologic findings and by reviewing surgical records. Among the 74 bowel resection operations, 44 were directly related to ileal lesions and 30 to ileocolonic or colonic lesions. Although all operations related to ileocolonic or colonic lesions were predicted by physicians at least 2 weeks prior to surgery, 25% of the operations (11/44) related to ileal lesions were not predicted in time by the physicians (p=0.005).

Table 2. Univariate Analysis of the Association between C-Reactive Protein Concentration and Various Parameters in Crohn's Disease Patients at the Time of Diagnosis: Chi-Square Test

Parameter	Normal CRP (n=95)	Elevated CRP (n=340)	p-value
WBC count, /mm^3			
<10,000	88	273	0.005
≥10,000	7	67	
Platelet count, /mm^3			
<350,000	72	146	<0.001
≥350,000	23	194	
ESR, mm/hr*			
≤20	60	64	<0.001
>20	28	265	
Serum albumin, g/dL			
≥3.3	84	170	<0.001
<3.3	11	170	
CDAI*			
Inactive (≤150)	34	37	<0.001
Mild (>150 and ≤220)	28	80	
Moderate (>220 and ≤450)	24	189	
Severe (>450)	2	19	
Disease location			
Ileal	50	62	<0.001
Colonic	3	27	
Ileocolonic	42	251	
Upper GI modifier*			
Absent	76	266	0.720
Present	18	70	
Disease behavior			
Inflammatory	67	259	0.492
Stricturing	16	43	
Penetrating	12	38	
Perianal fistula			
None or healed	85	266	0.016
Active	10	73	

CRP, C-reactive protein; WBC, white blood cell; ESR, erythrocyte sedimentation rate; CDAI, Crohn's disease activity index; GI, gastrointestinal.
*At the time of diagnosis, ESR, CDAI, and data for the upper GI modifier were not available in 18, 22, and 5 patients, respectively.

All 11 unpredicted operations were due to acute abdomen and/or bowel perforation during clinically stable follow-up periods. Acute abdomen and/or bowel perforation was a more frequent indication for surgery in operations for ileal than for ileocolonic or colonic lesions (p=0.070). The maximal presurgical CRP concentration was significantly lower in patients undergoing operations for ileal than for ileocolonic or colonic lesions (3.88±4.15 mg/dL vs 7.28±6.58 mg/dL, p=0.008) (Table 4).

DISCUSSION

Serum CRP concentration has been regarded as a serologic disease activity marker of CD. However, two previous studies suggested that the clinical significance of serum CRP may depend on disease location.[2,6] A retrospective analysis of 104 CD patients in the Mayo Clinic database showed that moderate to severe clinical activity, active lesions at colonoscopy, and histologically active inflammation were significantly associated with elevated CRP in CD patients. By contrast, abnormal radiologic findings in the small bowel were not associated with elevated

Table 3. Multivariate Analysis of Factors Predictive of an Elevated CRP at the Time of Diagnosis in Patients with Ileocolonic/Colonic Crohn's Disease (CD) and Ileal CD Based on a Logistic Regression Model

	Odds ratio (95% CI)	p-value
In patients with ileocolonic/colonic CD		
ESR, mm/hr		
<20	Reference	
≥20	5.033 (2.402–10.544)	<0.001
Serum albumin, g/dL		
≥3.3	Reference	
<3.3	4.184 (1.454–12.042)	0.008
CDAI		
Inactive (≤150)	Reference	
Mild (>150 and ≤220)	3.741 (1.494–9.370)	0.005
Moderate to severe (>220)	4.824 (1.911–12.181)	0.001
In patients with ileal CD		
ESR, mm/hr		
<20	Reference	
≥20	9.324 (3.443–25.247)	<0.001
Serum albumin, g/dL		
≥3.3	Reference	
<3.3	6.488 (1.932–9.594)	<0.001
CDAI		
Inactive (≤150)	Reference	
Mild (>150 and ≤220)	0.489 (0.116–2.063)	0.330
Moderate to severe (>220)	20.250 (0.593–6.914)	0.260

CI, confidence interval; ESR, erythrocyte sedimentation rate; CDAI, Crohn's disease activity index.

Table 4. Association between Physician's Prediction of Surgery and the Sites of Lesions Related to Surgery in Patients with Crohn's Disease

Site of the lesions related to surgery	Ileum (n=44)	Ileocolon or colon (n=30)	p-value
Interval from diagnosis to operation, mo	48.0±48.1	58.5±56.4	0.395
Median (range)	27.2 (0–177.4)	47.9 (0–211.8)	
Indication of operation			
Acute abdomen/perforation	12 (27.3)	3 (10.0)	0.070
Others	32 (72.7)	27 (90.0)	
Disease location 6 mo prior to surgery			
Ileal	23 (52.3)	0	NA
Colonic	0	1 (3.3)	
Ileocolonic	21 (47.7)	29 (96.7)	
Prediction of upcoming surgery			
Predicted*	33 (75.0)	30 (100)	0.005
Not predicted	11 (25.0)	0	
Maximal CRP level before surgery, mg/dL†	3.88±4.15	7.28±6.58	0.008

Data are presented as mean±SD or number (%).
NA, not applicable; CRP, C-reactive protein.
*'Predicted' surgery was defined as an operation performed after being recommended by the physician or after consultation with a surgeon at least 2 weeks prior to the surgery date; †Maximal CRP concentration measured from 6 months to 2 weeks before surgery.

CRP.[2] In another study, clinically active CD patients with low CRP level (n=22) had almost exclusively ileal disease location.[6] These results suggested that the serum CRP concentrations may have a weak or no association with disease activity in patients with ileal CD. However, because these studies included data obtained during follow-up of CD, they could not exclude fibrostenotic ileal lesions with no or minimal inflammation and did not compensate the influence of treatment response on the CRP concentration. Therefore, to clarify the weak association of CRP concentration and disease activity in ileal CD, it was necessary to minimize the influence of fibrostenotic lesions and treatment response. For this reason, we solely included CD patients who had never been treated before, and revealed that serum CRP concentration had a weaker association with disease activity in patients with ileal than ileocolonic or colonic CD. A recent study suggested that high sensitivity (hs)-CRP can reflect disease activity well and predict clinical relapse in CD during follow-up.[11] Comparable to our study, hs-CRP positivity was less common in ileal CD (43.2%) than in colonic (70%) or ileocolonic (72.6%) CD even in that study. However, the subgroup analysis was not performed in that study to evaluate the association between hs-CRP at diagnosis and disease activity. Therefore, further investigations are necessary to assure the usefulness of hs-CRP as a disease activity marker in ileal CD.

We also found that preoperative serum CRP concentrations were lower in CD patients who underwent bowel resection surgery due to ileal lesions than in patients with ileocolonic or colonic lesions. Moreover, all the operations directly related to ileocolonic or colonic lesions were predicted, while 25% of operations related to ileal lesions were not predicted in time by physician. Although a prospective population-based study found that elevated CRP (>5.3 mg/dL) at diagnosis in ileal CD may be a risk factor for subsequent surgery,[12] it is not well known if the follow-up CRP concentrations can help to predict impending surgery or not. Our results suggest that follow-up CRP concentrations may not be predictive of subsequent surgery, especially in CD patients whose main lesion is confined to the ileum. The most frequent cause of unexpected surgery in ileal CD patients was bowel perforation, suggesting that even clinically stable patients with relatively low or normal CRP concentrations are at risk for bowel perforation. Considerable part of the "unpredicted" surgical cases in ileal CD might have clinically insignificant fibrostenotic lesions until acute abdomen or perforation occurs as a result of aggravation of stenosis. However, because of the retrospective study design, we could not demonstrate the preoperative nature of the lesion in each patient by using recently highlighted imaging modality such as magnetic resonance enterography which might give more detailed information about the activity and nature of the small bowel lesions in CD.[13]

Another limitation of this study was the lack of patients with colonic CD within our cohort. Only 30 colonic CD patients were available for our study and it was impossible to confirm the statistical difference of Pearson correlation coefficients of CRP and CDAI according to disease location.

The exact mechanism underlying the differences in CRP concentrations according to lesion location is not yet well understood. Single nucleotide polymorphisms (SNPs) in CRP and CRP promoter genes may affect baseline or follow-up CRP concentrations in individual patients. An analysis of SNPs in the *CRP* gene and *CRP* promoter region in 164 CD patients found that,

in patients with active CD (CDAI >150), *CRP* 717 wild type (WT) status was associated with significantly higher hs-CRP concentrations than was 717 non-WT status. In addition, SES-CD was strongly correlated with various inflammatory markers, including hs-CRP, fecal calprotectin, fecal lactoferrin, and IL-6 in patients with active colonic CD, whereas no significant correlation was observed between SES-CD and these inflammatory markers in patients with inactive ileal CD. That study, however, did not assess the frequency of *CRP* 717 non-WT status in patients with ileal CD.[3]

Markers other than CRP may indicate disease activity in patients with CD. Fecal calprotectin and fecal lactoferrin are major components of secondary granules in polymorphonuclear cells and noninvasive inflammatory markers in the intestine.[14,15] Fecal calprotectin was found to be more closely correlated with SES-CD than were CRP, blood leukocytes, and CDAI.[16] However, in that study, the mean fecal calprotectin concentration was lower in patients with ileal than with ileocolonic CD, suggesting that this protein has limited usefulness as a marker of disease activity in patients with ileal CD. Moreover, the ability of fecal calprotectin to predict relapse in IBD was lower in patient with ileal than with ileocolonic CD.[17] Fecal calprotectin and lactoferrin were shown to be more sensitive predictors of endoscopically active CD than CDAI and CRP.[5] Subsequently, however, these fecal markers were shown to correlate significantly with endoscopic activity score and histologic score only in patients with ileocolonic and colonic CD, not in patients with ileal CD.[18] By contrast, fecal calprotectin was found to be more diagnostically accurate than CRP in predicting abnormal radiologic findings in the small bowel.[19] Further investigations are required to assess the correlation between disease activity in patients with ileal CD and fecal inflammatory markers.

In conclusion, our analysis of a relatively large number of Korean CD patients showed that the correlation between CRP concentration and disease activity was relatively weak in patients with ileal CD. This result is in good agreement with previous findings, showing that the correlation between serum CRP and disease activity was weaker in patients with ileal than with ileocolonic or colonic CD. Therefore, the usefulness of serum CRP as a disease activity marker in patients with ileal CD is limited, not only at diagnosis but also during follow-up.

CONFLICTS OF INTEREST

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Dong-Hoon Yang reviewed the medical records, collected the data, performed statistical analysis, and wrote the manuscript. Suk-Kyun Yang planned this study, reviewed the medical records, and collected the clinical data. He also supervised Dong-Hoon Yang performing statistical analysis and writing the manuscript. Sang Hyoung Park, Ho-Su Lee, Sun-Jin Boo, Jae-Ho Park, and Soo Young Na involved in reviewing the medical records, collecting the data, and writing the draft. Kee Wook Jung, Kyung-Jo Kim, Byong-Duk Ye, Jeong-Sik Byeon, Seung-Jae Myung, and Jin-Ho Kim were involved in planning this study and also supervised performing the statistical analysis and reviewing the initial draft.

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