# Serum X-C Motif Chemokine Ligand 1 Is Associated with Endoscopic Activity in Crohn's Disease: A Clinical Biomarker Study

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## ABSTRACT

***Background/Aims:*** *Monitoring endoscopic inflammation in Crohn's disease (CD) is difficult. This study examined whether X-C motif chemokine ligand 1 (XCL1) is associated with endoscopic activity, as defined by the Simple Endoscopic Score for Crohn's Disease (SES-CD).*

***Materials and Methods:*** *This was a single-center observational biomarker study. Peripheral blood mononuclear cell (PBMC) transcriptome sequencing was performed in 6 patients with newly diagnosed CD and 6 controls without inflammatory bowel disease. XCL1 protein expression was evaluated using immunohistochemistry and western blotting in 12 intestinal biopsy samples. Serum XCL1 levels were measured using enzyme-linked immunosorbent assay in 125 patients with CD and 40 controls. Patients with CD were classified according to the SES-CD. Correlation, logistic regression, receiver operating characteristic, bootstrap validation, and treatment-adjusted analyses were performed.*

***Results:*** *XCL1 was upregulated in PBMCs and increased in the intestinal mucosa of patients with active disease. Serum XCL1 levels differed among controls and SES-CD groups ($P < .001$). In patients with CD, serum XCL1 correlated with SES-CD ($r = 0.692$), fecal calprotectin (FC) ($r = 0.573$), Crohn's Disease Activity Index ($r = 0.420$), and C-reactive protein (CRP) ($r = 0.433$; all $P < .001$). XCL1 remained associated with endoscopic activity after adjustment (odds ratio = 1.005, 95% CI= 1.001-1.008, $P = .012$). The areas under the curve were 0.76 for XCL1, 0.81 for FC, and 0.85 for the XCL1+FC+CRP model.*

***Conclusion:*** *Although serum XCL1 was associated with SES-CD–defined endoscopic activity, its performance was lower than that of FC. XCL1 may serve as an exploratory adjunctive serum marker but requires further validation.*

***Keywords:*** *Biomarkers, Crohn disease, C-reactive protein, endoscopy, fecal calprotectin, X-C motif chemokine ligand 1*

## INTRODUCTION

Crohn's disease (CD) is a relapsing form of inflammatory bowel disease (IBD) that may affect any part of the gastrointestinal tract and is characterized by transmural inflammation.[1] Although CD has historically been less common in China than in Western countries, recent epidemiological data indicate an increasing burden of IBD in China, and regional evidence from coastal China suggests that CD is being recognized more frequently in areas undergoing rapid industrialization.[2,3] Current management increasingly depends on objective evidence of inflammatory control because symptoms alone may not reflect mucosal disease activity or future risk.[1,4] The Selecting Therapeutic Targets in Inflammatory Bowel Disease-II (STRIDE-II) consensus also emphasizes that clinical remission is insufficient as the sole treatment target and that objective assessment of inflammation remains necessary.[4] However, in routine care, repeated endoscopy is invasive, costly, and not always acceptable to patients. Therefore, accessible biomarkers of mucosal inflammation may be useful for disease monitoring.

Fecal calprotectin (FC) and C-reactive protein (CRP) are widely used in clinical practice. FC is more closely linked to luminal mucosal inflammation, whereas CRP reflects the systemic acute-phase response; both are useful but incomplete markers for monitoring CD activity.[5,6] FC testing may be limited by stool sample collection and turnaround time, whereas CRP may remain low in some patients despite active intestinal inflammation.[6] Other noninvasive markers, including serum hepcidin, red cell distribution width, leucine-rich alpha-2 glycoprotein, serum biomarker

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panels, and the Endoscopic Healing Index, have also been evaluated for IBD activity.[7-11] However, biomarker performance varies according to disease location, inflammatory burden, disease behavior, and clinical setting.

Chemokine-mediated immune-cell recruitment is closely related to mucosal inflammation in CD. Single-cell studies have described changes in immune-cell composition in the intestinal mucosa and peripheral blood of patients with IBD, together with disease-specific transcriptional alterations in CD mucosa.[12,13] X-C motif chemokine ligand 1 (XCL1) is predominantly produced by activated CD8+ T cells and NK cells, whereas its receptor, X-C motif chemokine receptor 1 (XCR1), is selectively expressed on cross-presenting conventional type 1 dendritic cells involved in cytotoxic T-cell priming.[14]

Previous studies have linked the XCL1–XCR1 axis to intestinal immune homeostasis and region-specific dendritic cell regulation.[15,16] These findings provide a biological basis for examining XCL1 in immune-mediated intestinal inflammation. However, most available evidence relates to intestinal immune regulation or non-CD inflammatory settings, and whether XCL1 is clinically associated with endoscopic disease activity in CD remains unclear.

Evidence regarding XCL1 in CD remains limited. Whether XCL1 changes consistently in peripheral blood mononuclear cells (PBMCs), intestinal mucosal tissues, and serum, and whether these changes relate to Simple Endoscopic Score for Crohn's Disease–defined endoscopic activity, requires further clarification. Its relationship with established markers such as FC and CRP also requires evaluation. The authors therefore measured XCL1 using PBMC transcriptomic screening, intestinal tissue validation, and serum analysis in an expanded clinical cohort. The main aim was to explore whether XCL1 could provide adjunctive information for the noninvasive assessment of endoscopic activity in CD.

### Main Points

- *Peripheral blood mononuclear cell transcriptome screening and tissue-level validation suggested increased X-C motif chemokine ligand 1 (XCL1) expression in Crohn's disease (CD).*
- *Serum XCL1 levels were higher in patients with CD with endoscopic activity and increased with disease severity.*
- *Serum XCL1 was positively correlated with Simple Endoscopic Score for Crohn's Disease and conventional inflammatory markers, including fecal calprotectin (FC) and C-reactive protein (CRP).*
- *XCL1 may be a candidate supplementary serum marker, particularly when interpreted in conjunction with FC and CRP.*

## MATERIALS AND METHODS

### Study Design and Participants

This single-center observational study was conducted at Yancheng First Hospital, between March 2025 and December 2025. Consecutive hospitalized patients with CD and contemporaneous non-IBD controls were enrolled under a prespecified sampling protocol, and clinical data were obtained from inpatient records and examination reports. The study included 4 linked phases: PBMC transcriptomic discovery, intestinal mucosal tissue validation, a small serum pilot experiment, and expanded clinical validation. Reporting was checked against the Strengthening the Reporting of Observational Studies in Epidemiology guidance for observational studies.

In the discovery phase, PBMC samples from 6 newly diagnosed patients with CD and 6 non-IBD controls were used for transcriptome sequencing. In the tissue validation phase, 12 intestinal mucosal samples were collected, with 3 samples each from the control, mild, moderate, and severe activity groups. A small serum pilot experiment was then performed to confirm the detectability of XCL1 in peripheral serum. The expanded validation cohort included 165 participants, consisting of 125 patients with CD and 40 non-IBD controls.

CD was diagnosed by experienced clinicians according to established guidelines, using clinical manifestations together with endoscopic, imaging, and histopathological findings.[17] Non-IBD controls were contemporaneous asymptomatic inpatients admitted for noninflammatory routine gastrointestinal evaluation and endoscopy. Medical records and routine laboratory results were reviewed, and individuals with evidence of active infection at any site, recent surgery or trauma, malignancy, autoimmune or systemic inflammatory disease, severe cardiac, hepatic, or renal dysfunction, incomplete key data, or endoscopic findings of polyps, IBD, infectious enteritis, intestinal tumors, or other definite inflammatory intestinal lesions were excluded. Serum samples from non-IBD controls were collected before endoscopy. Patients with CD were excluded if they had another type of IBD intestinal infection; intestinal tuberculosis; malignancy; severe cardiac, hepatic, or renal dysfunction; definite autoimmune disease; recent systemic infection; or incomplete key clinical data.

This study was approved by the Ethics Review Committee of Yancheng First Hospital (Ethics approval number: 2025-K-062; Date of approval: March 17, 2025). The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants. No Artificial Intelligence Tool was used in the preparation of the manuscript.

### *Clinical Data Collection and Assessment of Endoscopic Activity*

The expanded clinical validation cohort included 165 participants: 40 non-IBD controls, 38 patients in endoscopic remission, 39 with mild activity, and 48 with moderate-to-severe activity. Collected variables included sex, age, age at diagnosis, SES-CD score, Montreal classification, Crohn's Disease Activity Index (CDAI), history of abdominal surgery, perianal disease, body mass index (BMI), albumin (ALB), neutrophil-to-lymphocyte ratio (NLR), platelet count (PLT), erythrocyte sedimentation rate (ESR), CRP, FC, and treatment regimen.[17-20] Because treatment may influence inflammatory markers and endoscopic activity, treatment distribution was reported in the baseline table and considered when interpreting the results and performing sensitivity analyses.

Endoscopic disease activity was the primary outcome. The SES-CD assesses ulcer size, ulcerated surface, affected surface, and strictures in CD. According to the original SES-CD system and the prespecified criteria used in this study, scores of 0 to 2 were defined as endoscopic remission, 3 to 6 as mild activity, 7 to 15 as moderate activity, and greater than 15 as severe activity.[17,18] In this study, SES-CD scores of 0 to 2 indicated endoscopic remission only and did not necessarily indicate complete mucosal or transmural healing. Because both moderate and severe activity represent definite active disease, participants with SES-CD scores of 7 or greater were combined into a moderate-to-severe activity group in the expanded validation phase to improve statistical stability. In logistic regression and receiver operating characteristic (ROC) analyses, SES-CD scores of less than 3 were defined as endoscopic remission and scores of 3 or greater as endoscopic activity. SES-CD scoring was first performed independently by 2 experienced physicians who were blinded to serological results. Inter-rater reliability for the initial SES-CD scores was assessed using a 2-way random-effects intraclass correlation coefficient for absolute agreement. Disagreements were then resolved by discussion, and the final consensus score was used for analysis. Colonoscopy and serum sampling were completed during the same hospitalization to reduce temporal bias.

### *Peripheral Blood Mononuclear Cell Transcriptome Sequencing and Differential Expression Analysis*

In the discovery phase, peripheral blood was collected from selected participants, and PBMCs were isolated. Total RNA was extracted, assessed for quality, and used for messenger RNA library construction. Library construction and sequencing were performed by Novogene (Beijing, China) on an Illumina NovaSeq 6000 platform. Filtered reads were aligned to hg38 and analyzed at the gene level using DESeq2. Differentially expressed genes were defined as those with an adjusted $P$ value <.1 and an absolute $|\log2FoldChange| \geq 0.58$. XCL1 was selected for subsequent validation based on a combination of criteria: differential upregulation in CD, its role in chemokine-mediated immune-cell communication, the biological relevance of the XCL1–XCR1 axis to dendritic cell and T-cell interactions, and its suitability for serum measurement as a secreted chemokine. Given the small discovery sample, this selection was considered hypothesis generating and was followed by tissue and serum validation.

### *Detection of X-C Motif Chemokine Ligand 1 in Intestinal Mucosal Tissues*

During the tissue validation phase, intestinal mucosal tissues were obtained by colonoscopic biopsy. In patients with CD, biopsy specimens were obtained from the ileocecal region or from the colonic mucosal area with the most evident inflammation. Control tissues were obtained from intestinal mucosa without evident inflammatory changes. The samples were used for immunohistochemical and western blot analyses of XCL1 expression.

For immunohistochemistry, paraffin sections underwent citrate-buffer antigen retrieval (pH 6.0; Elabscience, Wuhan, China) and were incubated overnight at 4°C with an anti-XCL1 antibody (Proteintech, Rosemont, IL, USA; dilution 1 : 250), followed by standard secondary-antibody detection, diaminobenzidine development, and hematoxylin counterstaining. Representative images were captured using a bright-field microscope (Olympus, Tokyo, Japan). For each section, 1 low-magnification image and 1 enlarged image were obtained at 20× magnification, with scale bars of 50 μm and 20 μm, respectively. Two observers blinded to clinical grouping independently evaluated the staining. Mean optical density of XCL1-positive staining was measured using ImageJ for semiquantitative analysis.

Western blotting was used to evaluate XCL1 protein expression in intestinal mucosal tissues. Fresh mucosal tissues were lysed in radioimmunoprecipitation assay buffer (Beyotime, Shanghai, China), and protein concentration was measured using the bicinchoninic acid assay. Biological triplicates were analyzed for each group. Protein lysates were separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis and transferred to polyvinylidene fluoride membranes (Millipore, Burlington, MA, USA). Membranes were incubated with an anti-XCL1 antibody (Proteintech; dilution 1 : 3000) and β-actin monoclonal antibody (Proteintech, Wuhan, China; dilution 1 : 60000), followed by appropriate secondary antibodies. Bands were developed using an enhanced chemiluminescence substrate (NCM, Suzhou, China) and imaged using a ChemiDoc system (Bio-Rad, Hercules, CA, USA). ImageJ was used for densitometry, and relative XCL1 expression was calculated as the XCL1/β-actin grayscale ratio.

### *Serum X-C Motif Chemokine Ligand 1 Measurement and Collection of Clinical Laboratory Data*

In the expanded sample phase, fasting venous blood was collected, and serum was separated by centrifugation and stored at −80°C. Serum XCL1 was measured using a commercial enzyme-linked immunosorbent assay kit (Meimian, Dafeng, China). Standards and samples were processed according to the manufacturer's protocol. Absorbance was measured at 450 nm using an Infinite 200 PRO microplate reader (Tecan, Männedorf, Switzerland), and concentrations were calculated from the standard curve. CRP, FC, ESR, ALB, NLR, and PLT were obtained from routine laboratory tests performed during the same hospitalization.

### *Statistical Analysis*

Statistical analyses were performed using Statistical Package for the Social Sciences, version 26.0 (IBM SPSS Corp.; Armonk, NY, USA), and statistical graphs were generated using Python 3.10 (Python Software Foundation; Delaware, USA). Because this was an exploratory, single-center biomarker study based on consecutive eligible participants enrolled during a predefined period, no formal a priori sample size calculation was performed. A post hoc power analysis for serum XCL1 comparisons is provided in Supplementary Table 1. Continuous variables are summarized as medians with interquartile ranges because the main variables were skewed. Between-group comparisons were performed using Kruskal–Wallis tests, followed, when appropriate, by Holm-corrected Dunn post hoc comparisons. Categorical variables are summarized as counts and percentages and were compared using the chi-square test. Associations were assessed using Spearman rank correlation analysis. Univariate and multivariate logistic regression analyses used endoscopic activity (SES-CD ≥3) as the dependent variable; variables with $P < .05$ in univariate analysis were entered into the multivariate model using the enter method. Odds ratios (ORs) and 95% CIs were reported per original measurement unit for continuous variables. Model collinearity and calibration were assessed using the variance inflation factor and Hosmer–Lemeshow test, respectively. ROC analyses for endoscopic activity were restricted to patients with established CD, comparing SES-CD scores of less than 3 with scores of 3 or greater; non-IBD controls were not included when deriving activity-related cutoffs. ROC analysis evaluated individual markers and logistic regression–based combined models; single-marker cutoffs were determined using the Youden index. Bootstrap validation, treatment-adjusted sensitivity analysis, and DeLong tests were used to assess robustness. Exploratory comparisons of serum XCL1 according to treatment exposure were performed using the Mann–Whitney *U*-test. All tests were 2-sided, with $P < .05$ considered statistically significant.

## *RESULTS*

### *Peripheral Blood Mononuclear Cell Transcriptome Screening Identified X-C Motif Chemokine Ligand 1 as a Candidate Molecule*

In the discovery phase, PBMC samples from 6 newly diagnosed patients with CD and 6 non-IBD controls underwent transcriptome sequencing. The full list of differentially expressed genes is provided in Supplementary Table 2. Differential expression analysis identified a set of genes with altered expression in patients with CD. Because of the small sample size, these results were interpreted as exploratory. The volcano plot shows the overall distribution of differentially expressed genes, and the heatmap displays the expression patterns of candidate genes across the 2 groups (Figure 1). Among the differentially expressed chemokines, XCL1 was upregulated in patients with CD. The authors prioritized XCL1 for tissue validation and serum analysis because it was differentially expressed, biologically linked to XCR1-expressing dendritic cell and T-cell pathways, and measurable in serum as a secreted chemokine. The study workflow is shown in Figure. 1.

### *Tissue-Level Validation Showed Increased X-C Motif Chemokine Ligand 1 Expression in Crohn's Disease Intestinal Mucosa*

Twelve intestinal mucosal tissue samples were analyzed to examine XCL1 protein expression. Immunohistochemistry

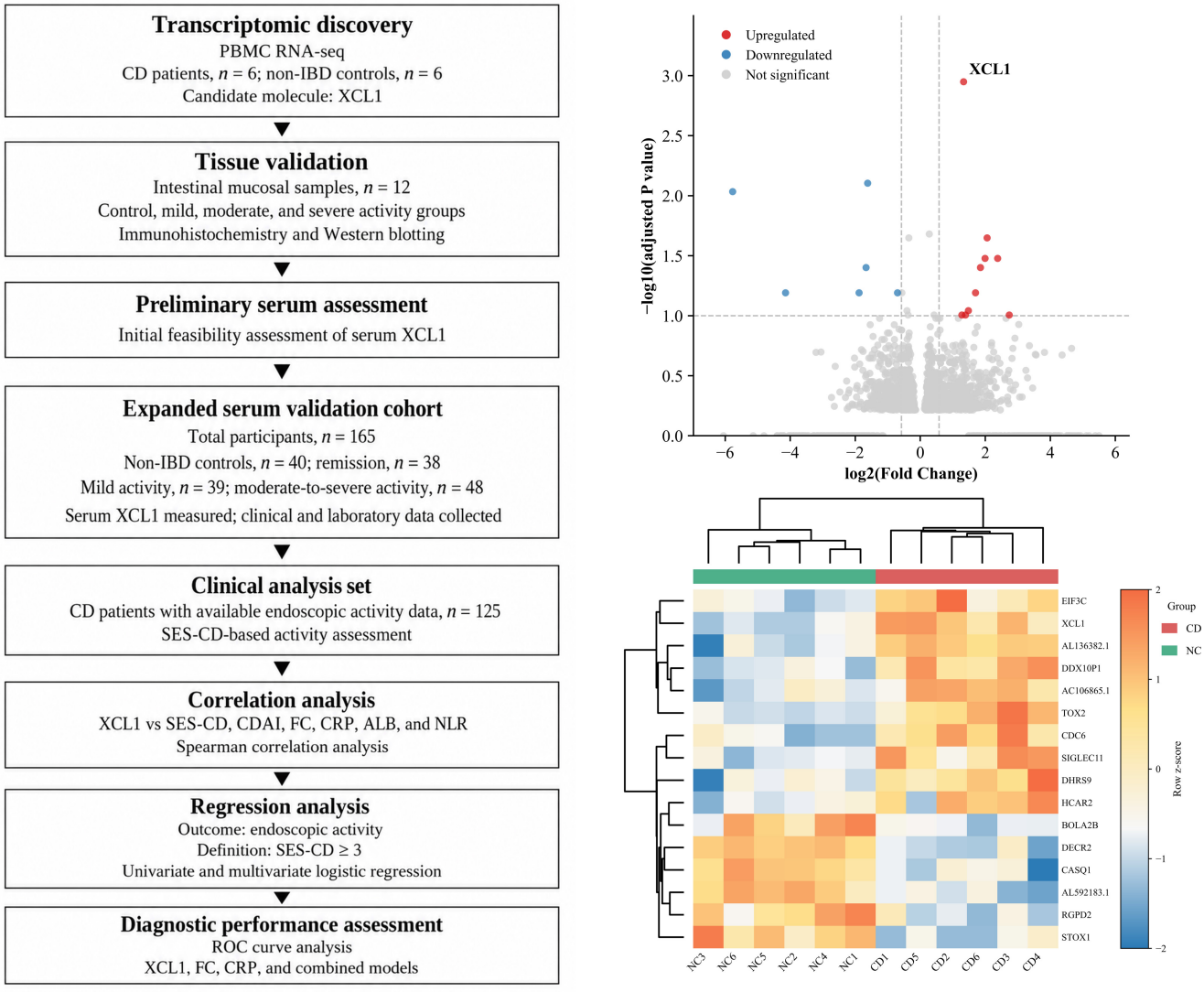


**Figure. 1.** PBMC transcriptome screening and study workflow. The workflow illustrates the discovery, tissue validation, serum pilot, and expanded clinical validation phases. The volcano plot shows differentially expressed genes between patients with CD and non-IBD controls. The heatmap displays screened differentially expressed genes after row-wise z-score normalization, with hierarchical clustering of genes and samples. CD, Crohn's disease; NC, non-IBD control; PBMC, peripheral blood mononuclear cell; XCL1, X-C motif chemokine ligand 1.

and western blotting both showed higher XCL1 expression in CD intestinal mucosa than in controls, with stronger expression in groups with greater SES-CD–defined activity (Figure 2). Because each tissue subgroup included only a small number of samples, these findings should be regarded as preliminary tissue-level support for the subsequent serum analysis.

### *Baseline Characteristics of the Expanded Cohort*

After the tissue validation and serum pilot experiments, an expanded clinical validation cohort was established, including 40 non-IBD controls, 38 patients in endoscopic remission, 39 with mild activity, and 48 with moderate-to-severe activity. Patients with CD were consecutively enrolled as inpatients. Before consensus review, the 2 blinded physicians showed excellent agreement in initial SES-CD scoring, with an intraclass correlation coefficient of 0.91 (95% CI: 0.87-0.93). Controls were asymptomatic inpatients admitted for noninflammatory routine gastrointestinal evaluation and endoscopy, without evident polyps, inflammatory intestinal lesions, or laboratory evidence of active systemic inflammation.

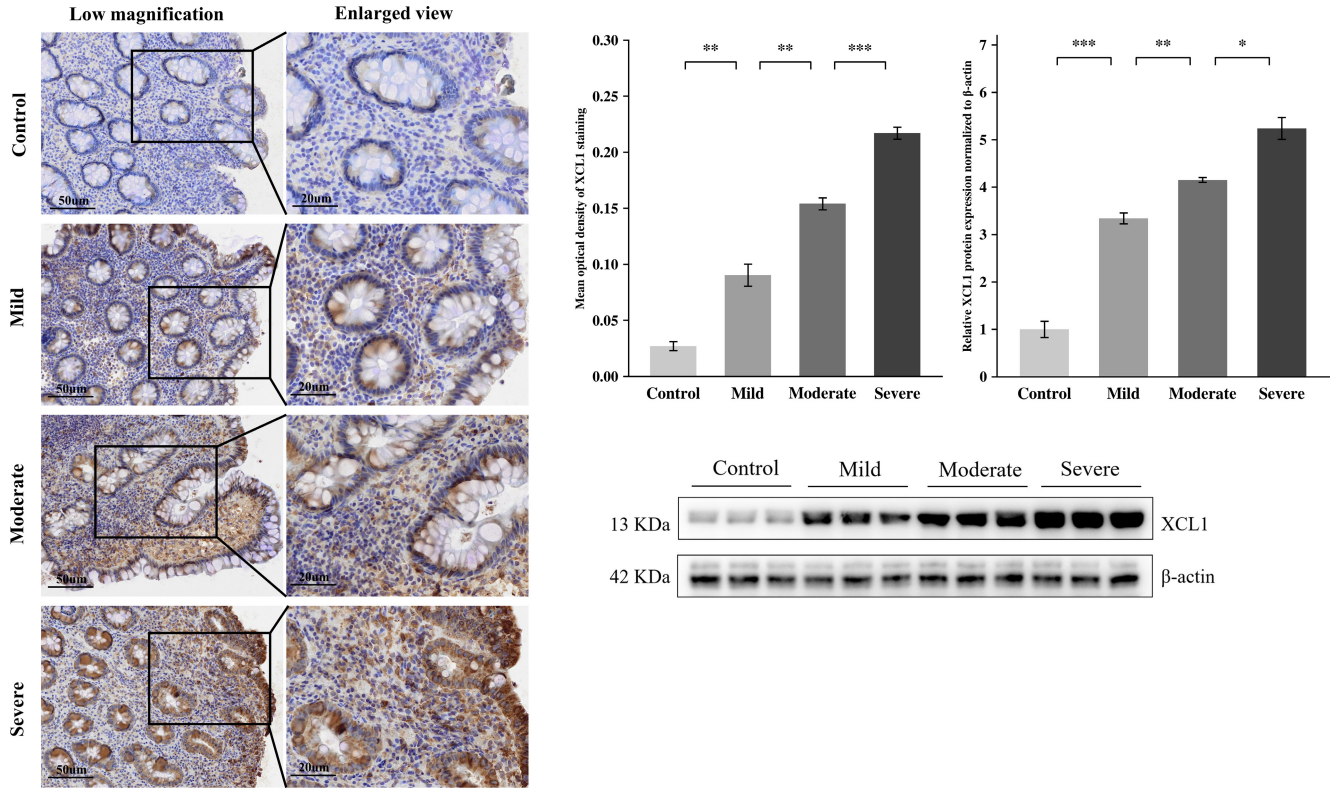


**Figure. 2.** Tissue-level validation of XCL1 expression in intestinal mucosal biopsy specimens. Disease activity was classified according to SES-CD. Representative immunohistochemical staining images of XCL1 are shown at low magnification and in enlarged views for each group. Scale bars indicate 50 μm and 20 μm, respectively. Semiquantitative analysis of XCL1 staining was performed using mean optical density. Representative western blotting bands of XCL1 and densitometric quantification of XCL1 protein expression normalized to β-actin are also shown. Error bars indicate standard deviation. **P* < .05; ***P* < .01; ****P* < .001. IHC, immunohistochemistry; SES-CD, Simple Endoscopic Score for Crohn's Disease; WB, western blotting; XCL1, X-C motif chemokine ligand 1.

Sex and age distributions did not differ significantly among the 4 groups (*P* = .856 and *P* = .273). Among CD subgroups, age at diagnosis, Montreal classification, perianal disease, history of abdominal surgery, and BMI were also similar (all *P* > .05). ALB was highest in remission and lower in active disease, whereas NLR and PLT tended to increase with disease activity. SES-CD, CDAI, XCL1, FC, CRP, and ESR differed significantly across groups. Corrected pairwise comparisons showed stepwise differences in SES-CD, CDAI, XCL1, FC, and CRP across CD activity strata.

Treatment regimens also differed across activity groups (*P* = .002), indicating a potential confounding factor that was considered in sensitivity analyses. Baseline and laboratory characteristics are shown in Table 1. In exploratory treatment-exposure analyses, serum XCL1 levels differed between patients receiving biologic and non-biologic therapy (*P* = .003). No significant differences were observed in anti-TNF–, ustekinumab-, or vedolizumab-containing treatment regimens (all *P* > .05; Supplementary Table 3). Given the very small vedolizumab subgroup, drug-specific comparisons should be interpreted descriptively.

### *Serum X-C Motif Chemokine Ligand 1 Was Associated with the Degree of Endoscopic Activity*

In the expanded cohort, serum XCL1 differed significantly among non-IBD controls, remission, mild activity, and moderate-to-severe activity groups (*P* < .001), with a gradual increase across SES-CD–defined activity strata. Pairwise comparisons showed higher XCL1 levels in all CD subgroups than in controls and significant differences among the 3 CD activity subgroups, supporting an association between serum XCL1 and SES-CD–defined endoscopic activity (Table 1).

Conventional inflammatory markers showed different patterns. FC increased stepwise with disease activity,

whereas CRP was most clearly elevated in moderate-to-severe disease. ESR mainly separated controls from CD subgroups and showed less consistent variation across CD activity strata (Table 1).

Spearman correlation analysis in the 125 patients with CD showed that serum XCL1 was positively correlated with SES-CD ($r$ = 0.692, $P$ < .001), CDAI ($r$ = 0.420, $P$ < .001), FC ($r$ = 0.573, $P$ < .001), and CRP ($r$ = 0.433, $P$ < .001). The strongest correlation was observed between serum XCL1 and SES-CD (Figure. 3).

### *X-C Motif Chemokine Ligand 1 Was Independently Associated with Endoscopic Activity and Showed Potential Value in Combined Models*

Logistic regression used endoscopic activity (SES-CD ≥3) as the binary outcome (Table 2). In univariate analysis, ALB, NLR, PLT, FC, CRP, and XCL1 were associated with endoscopic activity. After multivariable adjustment, ALB, FC, and XCL1 remained significant. ALB was protective (OR = 0.878, 95% CI: 0.792-0.974, $P$ = .014), whereas FC (OR = 1.014, 95% CI: 1.004-1.024, $P$ = .007) and XCL1 (OR = 1.005, 95% CI: 1.001-1.008, $P$ = .012) were associated with higher odds of activity. NLR, PLT, and CRP were no longer significant in the multivariate model. Model diagnostics showed no obvious multicollinearity or lack of fit (Supplementary Table 4). Because the model was not externally validated, its discrimination should be interpreted cautiously.

Among patients with CD, ROC curve analysis showed that FC had the highest AUC among single markers, with an AUC of 0.81 (95% CI: 0.73-0.89), sensitivity of 0.70, specificity of 0.89, and an optimal cutoff value of 166.57. XCL1 had an AUC of 0.76 (95% CI: 0.67-0.86), sensitivity of 0.89, specificity of 0.55, and an optimal cutoff value of 436.64. CRP had an AUC of 0.70 (95% CI: 0.59-0.81). For the combined models, AUCs were 0.82 for FC+CRP, 0.85 for XCL1+FC, 0.78 for XCL1+CRP, and 0.85 for XCL1+FC+CRP. Thus, XCL1 performed slightly worse than FC as a single marker but showed relatively high sensitivity. XCL1 did not outperform FC, and the incremental gain of XCL1-containing combined models over FC-based models was limited. Diagnostic performance metrics are summarized in Table 3, and the ROC curves are shown in Figure. 4. Bootstrap internal validation yielded AUCs broadly consistent with the main analysis. After treatment dummy variables were added, the treatment-adjusted model had an AUC of 0.873, which was not significantly different from the main model (AUC = 0.850, $P$ = .138) (Supplementary Table 5).

## *DISCUSSION*

The authors examined XCL1 in CD through PBMC transcriptomic screening, intestinal mucosal tissue validation, and serum analysis. XCL1 increased across these levels and was associated with SES-CD–defined endoscopic activity. These findings do not indicate that XCL1 can replace FC, CRP, or endoscopy or that it is clinically superior to FC. Rather, XCL1 should be viewed as an exploratory adjunctive serum marker related to current endoscopic activity.

The observed association is biologically reasonable. The XCL1–XCR1 axis contributes to interactions between dendritic cells and CD8+ T cells and has been implicated in intestinal immune homeostasis and local immune responses.[14-16] Evidence from other inflammatory disorders also supports a role for XCL1 in immune-cell recruitment and inflammatory injury. XCL1 has been detected in synovial fluid from patients with osteoarthritis and rheumatoid arthritis and has been linked to progenitor-cell recruitment.[21] The XCL1–XCR1 axis has also been implicated in T-cell-mediated inflammation after traumatic brain and spinal cord injury, and circulating XCL1 has been reported in HTLV-1-associated myelopathy and multiple sclerosis.[22,23] In diabetic nephropathy, XCL1 was shown to promote glomerular endothelial cell apoptosis and inflammatory responses.[24] Together, these studies support the biological plausibility of XCL1 as an inflammation-related chemokine, although they do not establish causality in CD. The authors' finding that XCL1 increased in PBMCs, intestinal mucosa, and serum is consistent with this background, but mechanistic interpretation remains cautious.

FC, CRP, and XCL1 appeared to reflect partly different inflammatory signals. FC is closely associated with luminal mucosal inflammatory burden, whereas CRP mainly reflects systemic inflammation. This interpretation is consistent with studies of FC and mucosal outcomes and with recent IBD studies comparing blood or serum markers with disease activity assessments.[5-8,25] Serum markers such as leucine-rich α-2 glycoprotein, the Endoscopic Healing Index, and broader serum protein panels have also been studied for endoscopic activity, but their performance varies according to disease location, behavior, and testing context.[9-11,26-30] Other multimarker strategies, including combined noninvasive markers of inflammatory activity, have also been proposed.[31] In this cohort, XCL1 showed a moderate correlation with FC and remained independently associated with endoscopic activity after adjustment, suggesting partial overlap without complete redundancy. XCL1 and FC may therefore provide related but different information. FC reflects

**Table 1.** Baseline Characteristics of Non-IBD Controls and Patients with Crohn's Disease Stratified by SES-CD

| Variables | Non-IBD Controls (n = 40) | Remission (n = 38) | Mild (n = 39) | Moderate to Severe (n = 48) | *P* |
|---|---|---|---|---|---|
| Gender, n (%) | | | | | |
| Male | 23 (57.5) | 24 (63.2) | 26 (66.7) | 29 (60.4) | .856 |
| Female | 17 (42.5) | 14 (36.8) | 13 (33.3) | 19 (39.6) | |
| Age | 38.0 (31.0-48.0) | 28.0 (21.0-37.0) | 42.0 (30.0-51.0) | 37.00 (31.0-45.0) | |
| Age at diagnosis | | 25.0 (20.0-34.5) | 33.0 (27.0-47.5) | 32.0 (23.0-41.5) | .273 |
| Montreal classification | | | | | .584 |
| A, n (%) | | | | | |
| A1 | | 7 (18.4) | 1 (2.6) | 5 (10.4) | .152 |
| A2 | | 23 (60.5) | 23 (59.0) | 27 (56.2) | |
| A3 | | 8 (21.1) | 15 (38.5) | 16 (33.3) | |
| L, n (%) | | | | | |
| L1 | | 5 (13.2) | 10 (25.6) | 5 (10.4) | .315 |
| L2 | | 5 (13.2) | 3 (7.7) | 4 (8.3) | |
| L3 | | 28 (73.7) | 26 (66.7) | 39 (81.2) | |
| L4 | | 0 (0.0) | 0 (0.0) | 0 (0.0) | |
| B, n (%) | | | | | |
| B1 | | 14 (36.8) | 14 (35.9) | 17 (35.4) | .241 |
| B2 | | 22 (57.9) | 18 (46.2) | 20 (41.7) | |
| B3 | | 2 (5.3) | 7 (17.9) | 11 (22.9) | |
| P, n (%) | | | | | |
| Yes | | 24 (63.2) | 25 (64.1) | 28 (58.3) | .836 |
| No | | 14 (36.8) | 14 (35.9) | 20 (41.7) | |
| SES-CD | | 1.0 (1.0-2.0) | 4.0 (3.0-5.0) | 10.5 (9.0-15.0) | |
| CDAI | | 87.0 (23.0-121.0) | 326.0 (262.0-376.0) | 396.0 (341.0- 455.0) | <.001 |
| History of abdominal surgery, n (%) | | | | | .28 |
| Yes | | 12 (31.6) | 16 (41.0) | 12 (25.0) | |
| No | | 26 (68.4) | 23 (59.0) | 36 (75.0) | |
| BMI (kg/m$^2$) | 21.4 (20.4-22.5) | 22.6 (19.8-25.1) | 21.1 (18.8-23.0) | 21.2 (18.4-23.7) | .349 |
| ALB (g/L) | 39.5 (37.9-41.2) | 43.2 (38.8-45.3) | 38.3 (33.5-42.5) | 36.7 (33.3-40.8) | <.001 |
| NLR | 2.1 (1.7-2.6) | 2.0 (1.7-2.6) | 2.6 (2.2-4.7) | 4.0 (3.1, 6.8) | <.001 |
| PLT (×10$^9$/L) | 207.5 (144.8-264.2) | 212.0 (183.2-255.8) | 236.0 (183.0-292.0) | 305.5 (220.2-382.2) | <.001 |
| XCL1 (pg/mL) | 172.5 (98.4-219.5) | 311.3 (226.8-427.6) | 516.5 (451.4-585.8) | 670.2 (531.4-801.2) | <.001 |
| FC (μg/g) | 37.1 (30.7-42.7) | 103.7 (83.5-154.9) | 154.3 (109.3-183.7) | 241.1 (192.0-287.5) | <.001 |
| CRP (mg/L) | 1.8 (0.8-3.4) | 4.5 (3.1-8.1) | 10.1 (4.2-14.3) | 16.2 (10.1-23.5) | <.001 |
| ESR (mm/h) | 5.9 (1.9-11.3) | 43.3 (36.9-48.6) | 40.5 (34.9-47.0) | 47.7 (42.7-55.5) | <.001 |
| Treatment, n (%) | | | | | .002 |
| MLS | | 4 (10.5) | 12 (30.8) | 27 (56.2) | |
| IFX | | 6 (15.8) | 4 (10.3) | 4 (8.3) | |

(*Continued*)

**Table 1.** Baseline Characteristics of Non-IBD Controls and Patients with Crohn's Disease Stratified by SES-CD (Continued)

| Variables | Non-IBD Controls (n = 40) | Remission (n = 38) | Mild (n = 39) | Moderate to Severe (n = 48) | *P* |
|---|---|---|---|---|---|
| ADA | | 3 (7.9) | 1 (2.6) | 2 (4.2) | |
| VDZ | | 1 (2.6) | 0 (0.0) | 1 (2.1) | |
| UST | | 20 (52.6) | 21 (53.8) | 9 (18.8) | |
| UST+UPA | | 4 (10.5) | 1 (2.6) | 5 (10.4) | |

Data are presented as median (IQR) or n (%). Kruskal–Wallis tests with Dunn–Holm correction were used for continuous variables, and chi-square tests were used for categorical variables. Detailed Holm-adjusted pairwise comparisons are provided in Supplementary Table 6.
ADA, adalimumab; ALB, albumin; BMI, body mass index; CDAI, Crohn's Disease Activity Index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FC, fecal calprotectin; IFX, infliximab; IQR, interquartile range; MLS, mesalazine; NLR, neutrophil-to-lymphocyte ratio; PLT, platelet count; SES-CD, Simple Endoscopic Score for Crohn's Disease; UPA, upadacitinib; UST, ustekinumab; VDZ, vedolizumab; XCL1, X-C motif chemokine ligand 1.

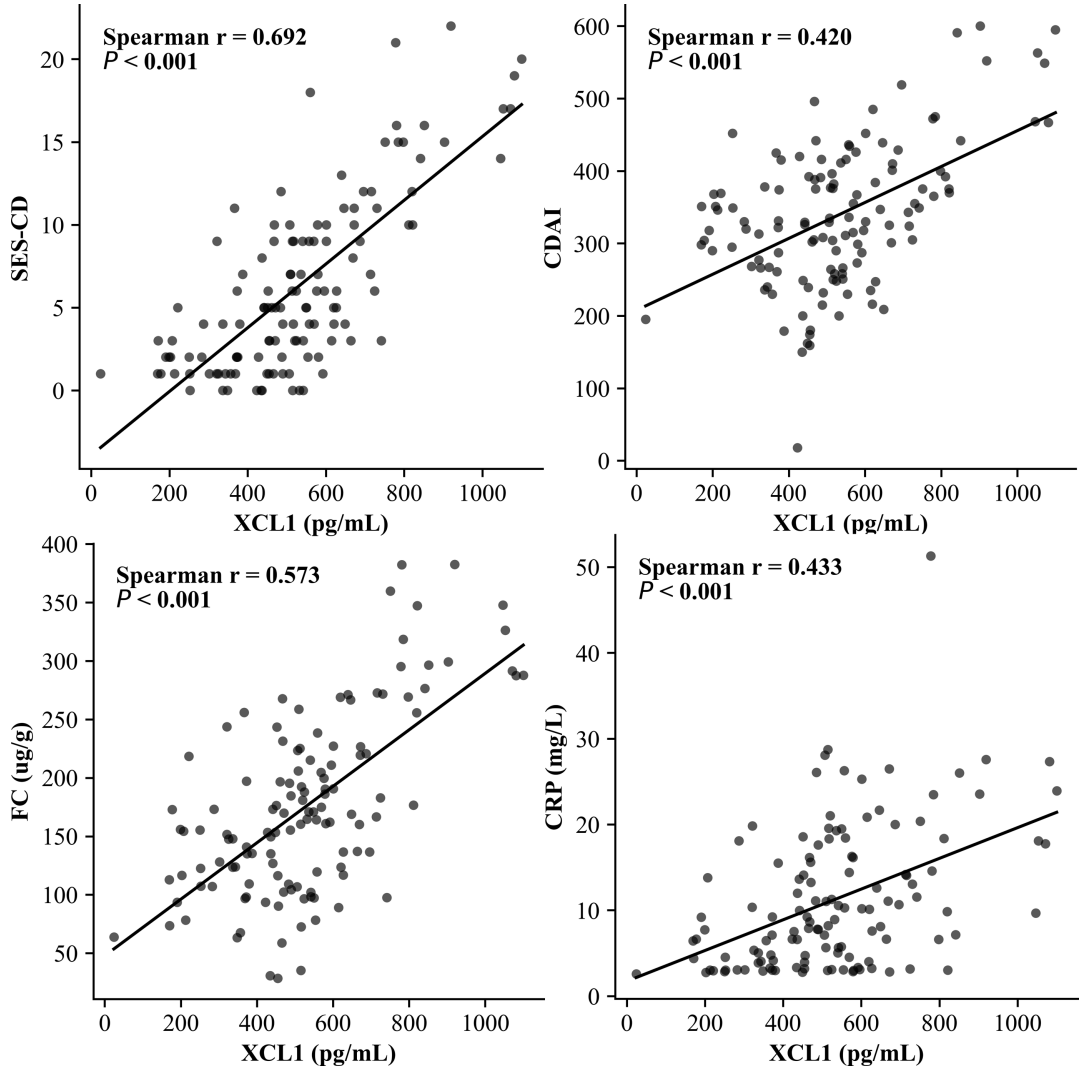


**Figure. 3.** Correlation analyses between serum XCL1 and clinical indicators in patients with Crohn's disease. The 4 image components show Spearman correlations of serum XCL1 with SES-CD, CDAI, FC, and CRP, respectively. CDAI, Crohn's Disease Activity Index; CD, Crohn's disease; CRP, C-reactive protein; FC, fecal calprotectin; SES-CD, Simple Endoscopic Score for Crohn's Disease; XCL1, X-C motif chemokine ligand 1.

**Table 2.** Univariate and Multivariate Logistic Regression Analyses for Endoscopic Activity in Crohn's Disease

| | Univariate | | Multivariate | |
|---|---|---|---|---|
| Variables | OR (95% CI) | *P* | OR (95% CI) | *P* |
| Gender | 1.003 (0.455-2.210) | .995 | | |
| Age at diagnosis | 1.008 (0.978-1.039) | .601 | | |
| History of abdominal surgery | 1.028 (0.453-2.332) | .947 | | |
| BMI | 0.888 (0.788-1.000) | .051 | | |
| ALB | 0.850 (0.784-0.921) | <.001 | 0.878 (0.792-0.974) | .014 |
| NLR | 1.954 (1.376-2.774) | <.001 | 1.475 (0.980-2.219) | .062 |
| PLT | 1.008 (1.003-1.013) | .004 | 1.004 (0.997-1.012) | .287 |
| FC | 1.020 (1.011-1.028) | <.001 | 1.014 (1.004-1.024) | .007 |
| CRP | 1.094 (1.032-1.160) | .003 | 1.031 (0.955-1.114) | .432 |
| ESR | 1.010 (0.978-1.043) | .545 | | |
| XCL1 | 1.006 (1.003-1.009) | <.001 | 1.005 (1.001-1.008) | .012 |

Variables with *P* < .05 in univariate analysis were entered into the multivariate logistic regression model.
ALB, albumin; BMI, body mass index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FC, fecal calprotectin; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio; PLT, platelet count; XCL1, X-C motif chemokine ligand 1.

neutrophil-associated inflammatory products released into the intestinal lumen, whereas XCL1, as a chemokine, may be more closely related to immune-cell interaction and persistence of local inflammation.

This difference is consistent with the heterogeneity of CD activity, which is shaped by mucosal inflammation, systemic inflammation, lesion distribution, and treatment status. The modest improvement after adding XCL1 suggests that XCL1, FC, and CRP may capture overlapping but not identical signals. In this study, XCL1 alone had a lower AUC than FC but higher sensitivity and lower specificity. Although XCL1 differed between remission and mild activity in corrected pairwise analysis, its single-marker AUC for identifying endoscopic activity remained moderate. This profile supports an exploratory adjunctive role for XCL1 rather than its use as a stand-alone clinical test for confirming endoscopic activity. Internal validation and treatment-adjusted analyses supported the main findings, but external validation and calibration assessment are still needed before its clinical utility can be determined. These analyses should be viewed as exploratory rather than clinically ready. Higher XCL1 levels in patients with CD in remission than in non-IBD controls suggest limited disease specificity. Because SES-CD scores of 0-2 do not necessarily indicate complete mucosal or transmural healing, residual immune activation may persist during remission.[1,32-34]

**Table 3.** ROC Curve Analysis of Individual and Combined Biomarkers for Identifying Endoscopic Activity

| Parameter | AUC (95% CI) | *P* | Cutoff | Sensitivity | Specificity | Youden Index |
|---|---|---|---|---|---|---|
| XCL1 | 0.76 (0.67-0.86) | <.001 | 436.64 | 0.89 | 0.55 | 0.44 |
| FC | 0.81 (0.73-0.89) | <.001 | 166.57 | 0.70 | 0.89 | 0.60 |
| CRP | 0.70 (0.59-0.81) | <.001 | 9.24 | 0.70 | 0.76 | 0.46 |
| FC+CRP | 0.82 (0.74-0.89) | <.001 | — | 0.72 | 0.84 | 0.57 |
| XCL1+FC | 0.85 (0.78-0.92) | <.001 | — | 0.78 | 0.76 | 0.54 |
| XCL1+CRP | 0.78 (0.69-0.87) | <.001 | — | 0.55 | 0.89 | 0.45 |
| XCL1+FC+CRP | 0.85 (0.78-0.92) | <.001 | — | 0.68 | 0.92 | 0.60 |

AUCs were calculated for identifying SES-CD–defined endoscopic activity (SES-CD ≥3) among patients with CD only. Optimal cutoff values for single markers were determined using the Youden index. Combined models were based on logistic regression–derived predicted probabilities and therefore were not assigned single biological cutoff values.
AUC, area under the curve; CRP, C-reactive protein; FC, fecal calprotectin; SES-CD, Simple Endoscopic Score for Crohn's Disease; XCL1, X-C motif chemokine ligand 1.

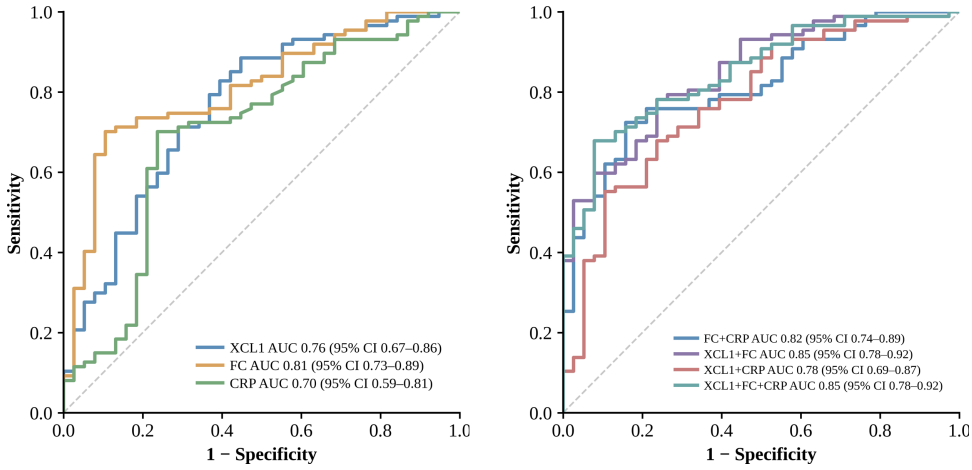


**Figure. 4.** ROC analysis of XCL1 and combined models for identifying endoscopic activity defined as SES-CD ≥3. The first panel shows ROC curves for serum XCL1, FC, and CRP. The second panel shows ROC curves for logistic regression–based combined models, including FC+CRP, XCL1+FC, XCL1+CRP, and XCL1+FC+CRP. AUC values are shown in the panels; combined models were not assigned single biological cutoff values. AUC, area under the curve; CRP, C-reactive protein; FC, fecal calprotectin; ROC, receiver operating characteristic; SES-CD, Simple Endoscopic Score for Crohn's Disease; XCL1, X-C motif chemokine ligand 1.

The study has several limitations. This was a single-center hospitalized cohort, and the non-IBD controls were endoscopy-based inpatients rather than community-based healthy volunteers. Although obvious inflammatory conditions were excluded based on clinical and laboratory information, unmeasured comorbidities or subclinical inflammation may still have affected baseline XCL1 levels. Therefore, control-related comparisons should be interpreted cautiously and externally validated. The PBMC discovery and tissue analyses were small, particularly the tissue cohort (n = 12, 3 per subgroup), so these findings should be considered exploratory supportive evidence rather than definitive biological validation. Treatment regimens differed across activity groups, and residual confounding by treatment exposure cannot be excluded despite sensitivity analyses. Finally, the cross-sectional design precluded evaluation of whether XCL1 predicts relapse, treatment response, hospitalization, surgery, mucosal healing, or endoscopic progression. Prospective multicenter studies are needed.

In this cohort, serum XCL1 was associated with current endoscopic activity in CD. As a single marker, it performed slightly lower than FC but showed relatively high sensitivity. XCL1-containing models showed numerical improvement but did not clearly outperform FC alone or FC+CRP. Therefore, XCL1 should be regarded as an exploratory adjunctive serum marker rather than a replacement for FC, CRP, or endoscopy.

***Data Availability Statement:*** The data that support the findings of this study are available on request from the corresponding author.

***Artificial Intelligence Usage Statement:*** The authors declared that no Artificial Intelligence Tool was used in the preparation of the manuscript.

***Ethics Committee Approval:*** Ethical committee approval was received from the Ethics Committee of Yancheng First Hospital (Approval no: 2025-K-062, Date: March 17, 2025).

***Informed Consent:*** Written informed consent was obtained from the patients who agreed to take part in the study.

***Peer-review:*** Externally peer-reviewed.

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***Author Contributions:*** Concept – J.C.; Design – J.C., Z.L.; Supervision – Y.C.; Resources – Y.C.; Materials – X.L.; Data Collection and Processing – Y.H., W.X.; Analysis and/or Interpretation – Z.L.; Literature Search – Z.L.; Writing – Z.L.; Critical Review – Y.C.

***Declaration of Interests:*** The authors have no conflicts of interest to declare.

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**Supplementary Table 1** Post hoc power analysis for serum XCL1 comparisons

| Analysis | Groups or comparison | Statistical result | Statistical power |
|---|---|---|---|
| Overall comparison of serum XCL1 levels | Non-IBD controls, endoscopic remission, mild activity, and moderate-to-severe activity (n = 165) | One-way ANOVA: $F$ (3, 161) = 98.71, $P$ < 0.001; $\eta^2$ = 0.65; Cohen's f = 1.36 | >99.9% |
| Pairwise comparison | Non-IBD controls vs active CD (SES-CD ≥3; n = 40 vs 87) | Cohen's d = 2.63 | >99.9% |

Post hoc power analysis was performed based on the observed differences in serum XCL1 levels. The overall comparison used the four-group structure adopted in the main analysis. The analysis was exploratory and was not used for prospective sample size planning. CD, Crohn's disease; IBD, inflammatory bowel disease; SES-CD, Simple Endoscopic Score for Crohn's Disease; XCL1, X-C motif chemokine ligand 1.

**Supplementary Table 2** Differentially expressed genes identified by PBMC RNA sequencing between patients with Crohn's disease and non-IBD controls

| Gene symbol | Gene ID | $\lvert\log_2\text{FoldChange}\rvert$ | $P$ value | Adjusted $P$ value | Regulation |
|---|---|---|---|---|---|
| XCL1 | ENSG00000143184 | 1.333 | 5.56E−8 | 0.001 | Upregulated |
| AC106865.1 | ENSG00000250771 | 2.056 | 5.97E−6 | 0.022 | Upregulated |
| HCAR2 | ENSG00000182782 | 1.993 | 1.25E−5 | 0.033 | Upregulated |
| DDX10P1 | ENSG00000237135 | 2.38 | 1.32E−5 | 0.033 | Upregulated |
| SIGLEC11 | ENSG00000161640 | 1.852 | 1.79E−5 | 0.04 | Upregulated |
| CDC6 | ENSG00000094804 | 1.699 | 4.45E−5 | 0.064 | Upregulated |
| DHRS9 | ENSG00000073737 | 1.481 | 7.38E−5 | 0.091 | Upregulated |
| AL136382.1 | ENSG00000285210 | 2.737 | 9.44E−5 | 0.099 | Upregulated |
| TOX2 | ENSG00000124191 | 1.279 | 9.56E−5 | 0.099 | Upregulated |
| EIF3C | ENSG00000184110 | 1.39 | 1.07E−4 | 0.099 | Upregulated |
| AL592183.1 | ENSG00000273748 | -1.618 | 7.78E−7 | 0.008 | Downregulated |
| BOLA2B | ENSG00000169627 | -5.77 | 1.37E−6 | 0.009 | Downregulated |
| CASQ1 | ENSG00000143318 | -1.667 | 1.96E−5 | 0.04 | Downregulated |
| DECR2 | ENSG00000242612 | -0.699 | 3.84E−5 | 0.064 | Downregulated |
| RGPD2 | ENSG00000185304 | -1.881 | 4.54E−5 | 0.064 | Downregulated |
| STOX1 | ENSG00000165730 | -4.143 | 4.78E−5 | 0.064 | Downregulated |

Differentially expressed genes were defined as genes with |log2FoldChange| > 0.58 and adjusted P value < 0.1. A total of 16 genes met the threshold. Positive log2FoldChange values indicate upregulation in the Crohn's disease group relative to non-IBD controls, whereas negative values indicate downregulation. Adjusted P values were used to control for multiple testing. DEG, differentially expressed gene; PBMC, peripheral blood mononuclear cell.

**Supplementary Table 3** Serum XCL1 levels according to treatment exposure in patients with Crohn's disease

| Comparison | Non-exposed group | n | XCL1, median (IQR) | Exposed group | n | XCL1, median (IQR) | P value |
|---|---|---|---|---|---|---|---|
| Biologic therapy | No | 43 | 601.0 (445.6, 764.4) | Yes | 82 | 488.5 (371.8, 576.3) | .003 |
| Anti-TNF therapy | No | 105 | 517.3 (436.6, 646.0) | Yes | 20 | 437.9 (316.1, 556.3) | .089 |
| UST-containing therapy | No | 65 | 536.1 (379.7, 713.5) | Yes | 60 | 507.3 (436.6, 578.8) | .167 |
| VDZ-containing therapy | No | 123 | 516.5 (404.9, 633.3) | Yes | 2 | 419.9 (396.1, 443.8) | .373 |

Only patients with Crohn's disease were included (n=125). Values are presented as median (IQR). P values were calculated using the Mann-Whitney U test. For biologic therapy, the exposed group included IFX, ADA, VDZ, UST, and UST+UPA; the non-exposed group included MLS. Drug-specific comparisons, especially for VDZ, should be interpreted cautiously because of the small subgroup size. ADA, adalimumab; IFX, infliximab; IQR, interquartile range; MLS, mesalazine; TNF, tumor necrosis factor; UPA, upadacitinib; UST, ustekinumab; VDZ, vedolizumab; XCL1, X-C motif chemokine ligand 1.

**Supplementary Table 4** Model Diagnostic Indices for Multivariate Logistic Regression

| Diagnostic index | Value |
|---|---|
| Selected variables for multivariate model | ALB, NLR, PLT, FC, CRP, XCL1 |
| AUC of multivariate model | 0.904 |
| Hosmer-Lemeshow goodness-of-fit *P* value | 0.792 |
| Maximum VIF | 1.629 |

AUC indicates model discrimination; the Hosmer-Lemeshow test was used to assess calibration; VIF was used to evaluate multicollinearity. ALB, albumin; AUC, area under the curve; CRP, C-reactive protein; FC, fecal calprotectin; NLR, neutrophil-to-lymphocyte ratio; PLT, platelet count; VIF, variance inflation factor; XCL1, X-C motif chemokine ligand 1.

**Supplementary Table 5.** Treatment-adjusted sensitivity analysis of ROC models.

| Analysis | n | AUC | Note |
|---|---|---|---|
| Main model: XCL1+FC+CRP | 125 | 0.85 | Reference |
| Treatment-adjusted model: XCL1+FC+CRP + Treatment dummies | 125 | 0.873 | DeLong *P* = 0.138 vs main model |

The treatment-adjusted sensitivity model added treatment-regimen dummy variables to the XCL1+FC+CRP model to evaluate robustness to treatment-factor adjustment. The DeLong P value compares the treatment-adjusted model with the main model. AUC, area under the curve; CRP, C-reactive protein; FC, fecal calprotectin; ROC, receiver operating characteristic; XCL1, X-C motif chemokine ligand 1.

**Supplementary Table 6** Pairwise Comparisons of Continuous Variables According to SES-CD Groups.

| Variables | SES-CD | CDAI | ALB | NLR | PLT | XCL1 | FC | CRP | ESR |
|---|---|---|---|---|---|---|---|---|---|
| Overall *P* value | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |
| Remission vs Mild | <0.001 | 0.02 | 0.001 | 0.005 | 0.677 | <0.001 | 0.007 | <0.001 | 0.41 |
| Remission vs Moderate-to-severe | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | 0.235 |
| Mild vs Moderate-to-severe | <0.001 | <0.001 | 0.518 | 0.023 | 0.021 | <0.001 | <0.001 | <0.001 | 0.043 |
| Non-IBD controls vs Remission | | | 0.094 | 0.841 | 0.677 | <0.001 | <0.001 | <0.001 | <0.001 |
| Non-IBD controls vs Mild | | | 0.316 | 0.003 | 0.196 | <0.001 | <0.001 | <0.001 | <0.001 |
| Non-IBD controls vs Moderate-to-severe | | | 0.098 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |

Only continuous variables with significant overall Kruskal-Wallis tests are shown. Values are Holm-adjusted P values from Dunn's post hoc pairwise comparisons. Blank cells indicate comparisons that were not applicable because the corresponding variable was not available for non-IBD controls. ALB, albumin; CDAI, Crohn's Disease Activity Index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FC, fecal calprotectin; NLR, neutrophil-to-lymphocyte ratio; PLT, platelet count; SES-CD, Simple Endoscopic Score for Crohn's Disease; XCL1, X-C motif chemokine ligand 1.