Research Square

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Association of CADM1 expression with inflammatory activity in ulcerative colitis

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Research Article

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Abstract

Background

This study aimed to investigate CADM1 protein expression in colonic mucosal biopsies from patients with ulcerative colitis (UC). We further assessed its associations with inflammatory activity, p-STAT3 activation, and CD11c-positive inflammatory cell infiltration.

Methods

A total of 108 colonic mucosal samples were included, comprising 13 controls and 95 UC patients. UC patients were classified as mild, moderate, or severe according to the Ulcerative Colitis Endoscopic Index of Severity (UCEIS). Histological inflammation was assessed using hematoxylin and eosin staining and the Nancy histological index (NHI). CADM1, p-STAT3, and CD11c expression was detected by immunohistochemistry and quantified using QuPath. Spearman correlation and receiver operating characteristic (ROC) curve analyses were performed. CADM1 and inflammation-related gene expression were further validated using GSE87466 and GSE75214.

Results

NHI differed significantly among the four groups and increased with disease severity. CADM1, p-STAT3, and CD11c expression was higher in UC mucosa than in controls and generally increased with endoscopic activity. CADM1 expression was positively correlated with UCEIS, modified Mayo score, NHI, p-STAT3, and CD11c. ROC analysis showed that CADM1, p-STAT3, CD11c, and their combined model had exploratory discriminatory ability for distinguishing UC from controls and severe UC from mild-to-moderate UC. GEO validation showed that CADM1 was upregulated in two independent UC cohorts, accompanied by increased STAT3, SOCS3, IL6, and TNF expression.

Conclusions

CADM1 expression is increased in UC colonic mucosa and is associated with inflammatory activity, p-STAT3 activation, and CD11c-positive inflammatory cell infiltration. CADM1 may serve as a tissue marker reflecting mucosal inflammation and local immune microenvironment changes in UC.

Introduction

Ulcerative colitis (UC) is a chronic, relapsing-remitting inflammatory bowel disease (IBD) that primarily affects the colonic and rectal mucosa, presenting as continuous and diffuse mucosal inflammation(1, 2). In recent years, the therapeutic strategy for UC has gradually shifted from symptom-based

management to a treat-to-target approach focusing on clinical remission and endoscopic healing, with increasing attention also given to controlling histological inflammation(3–5).

Currently, UC disease activity is primarily assessed based on clinical symptoms, laboratory parameters, endoscopic findings, and histological scores. Among these, the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) and the Nancy histological index (NHI) are commonly used to evaluate endoscopic and microscopic inflammation, respectively(6, 7). However, conventional scoring systems cannot directly reflect local mucosal inflammatory signaling or immune cell infiltration. Therefore, identifying tissue-level molecular markers may provide a complementary approach to assessing disease activity.

The development and progression of UC are closely associated with impaired intestinal epithelial barrier function, disrupted mucosal immune homeostasis, infiltration of myeloid inflammatory cells, and aberrant cytokine signaling(2, 8, 9). Studies have shown that in active UC mucosa, epithelial, stromal, and immune cells undergo significant remodeling. This indicates that inflammatory activity in UC not only involves mucosal structural damage but is also accompanied by alterations in the composition and spatial distribution of local immune cells(10, 11). Among these pathways, the IL-6/JAK/STAT3 axis and tumor necrosis factor (TNF)-related inflammatory responses are important contributors to mucosal inflammation in UC(9, 12). Phosphorylated signal transducer and activator of transcription 3 (p-STAT3) reflects the activation status of the STAT3 pathway. CD11c, also known as integrin alpha X (ITGAX), is commonly used as a marker for dendritic cells and a subset of myeloid inflammatory cells(13, 14).

Cell adhesion molecule 1 (CADM1) is a member of the immunoglobulin superfamily of cell adhesion molecules, also known as TSLC1, IGSF4, or NECL-2, and is involved in intercellular adhesion, maintenance of epithelial structure, and immune cell interactions(15–17).CADM1 can interact with class I-restricted T cell-associated molecule (CRTAM) and participate in immune responses involving natural killer cells and CD8 + T cells(18, 19).A recent study reported that CADM1 is upregulated in colonic tissues from patients with inflammatory bowel disease (IBD) and is primarily enriched in myeloid cell populations, including macrophages and dendritic cells. The study also reported an increased number of CADM1-positive myeloid cells in UC colonic tissue, which were spatially adjacent to CD8 + T cells. In addition, recombinant soluble CADM1 was shown to enhance STAT3 phosphorylation-associated proinflammatory signaling. However, the protein expression pattern of CADM1 in conventional UC colonic mucosal biopsy tissues, and its relationship with endoscopic activity, histological inflammation, p-STAT3 activation, and CD11c-positive cell infiltration, remains unclear(20).

Based on this, the present study combined immunohistochemistry (IHC), digital pathology quantification, and publicly available transcriptomic data from the Gene Expression Omnibus (GEO) to evaluate CADM1 expression in UC colonic mucosa. The study further examined its associations with inflammatory activity, p-STAT3 activation, and CD11c-positive cell infiltration, thereby assessing the potential of CADM1 as a tissue biomarker for mucosal inflammatory activity in UC.

Materials and methods

Study design and participants

This was a single-center retrospective study. Consecutive patients who were diagnosed with UC, underwent colonoscopy, and had colonic mucosal biopsy samples collected at Xiangyang No.1 People's Hospital, Hubei Province, China. between April 2024 and April 2026 were included. The control group included individuals who underwent colonoscopy during the same period, had no history of IBD, and showed no obvious inflammatory changes on endoscopic or pathological examination. A total of 108 colonic mucosal tissue samples were included, comprising 13 controls and 95 UC patients. All UC patients underwent assessment of endoscopic inflammatory activity. According to the UCEIS score, UC patients were classified into mild UC (n = 34), moderate UC (n = 32), and severe UC (n = 29) groups.

The inclusion criteria for UC patients were as follows: (1) meeting the diagnostic criteria for UC(21); (2) undergoing colonoscopy and having formalin-fixed paraffin-embedded (FFPE) colonic mucosal biopsy tissues available for pathological review and IHC analysis; (3) having complete endoscopic, pathological, and main clinical data; (4) having laboratory test results available within 7 days before or after colonoscopy.

The exclusion criteria were as follows: (1) concomitant Crohn's disease, unclassified IBD, infectious colitis, ischemic colitis, radiation colitis, or drug-related colitis; (2) concomitant colorectal cancer, intestinal lymphoma, or other malignancies; (3) insufficient biopsy tissue, severe tissue crush artifact, necrosis, tissue detachment, or poor staining quality that precluded reliable quantitative analysis; (4) incomplete clinical, endoscopic, or pathological data.

The control group included individuals who underwent colonoscopy during the same period, had no history of IBD, and showed no obvious inflammatory changes on endoscopic or pathological examination. The exclusion criteria for controls were as follows: (1) infectious colitis, intestinal tumors, ischemic bowel disease, radiation colitis, or other definite intestinal inflammatory diseases; (2) recent use of drugs that could markedly affect intestinal mucosal inflammation, such as systemic glucocorticoids, immunosuppressants, or biologics; and (3) biopsy tissue quality that did not meet the requirements for subsequent H&E staining, IHC staining, or digital pathology analysis.

This study was approved by the Ethics Committee of Xiangyang No.1 People's Hospital (approval number: 2025KY026). All study procedures were performed in accordance with the Declaration of Helsinki. As this was a retrospective study using only archived paraffin-embedded tissue samples and anonymized clinical data, without additional intervention, the requirement for written informed consent was waived by the ethics committee.

Clinical data collection

Demographic data, laboratory test results, and disease activity-related variables were collected for all participants. Demographic data included age and sex. Laboratory parameters included white blood cell

count (WBC), hemoglobin (Hb), platelet count (PLT), albumin (ALB), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR). Disease-related variables included disease extent according to the Montreal classification (E1, E2, and E3), UCEIS score, modified Mayo score, and NHI. The laboratory results closest to the time of colonoscopy were included in the analysis.

Tissue sampling, H&E staining, and NHI assessment

All UC patients underwent multi-site mucosal biopsies during colonoscopy. Considering that inflammation may vary across different sites in the same patient, the FFPE tissue from the site with the most severe lesion, confirmed by pathological review, was selected as the representative sample for H&E staining, IHC staining, and subsequent digital quantification. Paraffin sections were deparaffinized and rehydrated using standard procedures before H&E staining. Histological inflammatory activity was assessed using the NHI(7). All slides were independently evaluated by two pathologists with experience in gastrointestinal pathology, blinded to clinical data. Any discrepancies in scoring were resolved through joint review to reach a consensus.

Immunohistochemistry

FFPE tissue sections (4 μm thick) were deparaffinized, rehydrated, and subjected to heat-induced antigen retrieval using citrate buffer (pH 6.0). Endogenous peroxidase activity was blocked with 3% hydrogen peroxide, and nonspecific binding was blocked with goat serum. Sections were incubated overnight at 4°C with primary antibodies against CADM1 (Proteintech, 14335-1-AP, 1:150), p-STAT3 (Tyr705; Immunoway, YM8551, 1:600), and CD11c (Immunoway, YM8744, 1:500). The next day, corresponding secondary antibodies (AntGene, ANT020, 1:500) were applied, followed by 3,3'-diaminobenzidine (DAB) development. Sections were counterstained with hematoxylin, dehydrated, cleared, and mounted. All slides were processed under identical experimental conditions. Staining results were observed under a light microscope, and representative images were captured using a 20× objective lens. Scale bars were added to indicate 50 μm. CADM1 and CD11c positive signals appeared as brown-yellow staining, whereas p-STAT3 signals were primarily nuclear.

Quantitative analysis of immunohistochemistry

IHC-stained slides were digitally quantified using QuPath software(22). All slides were processed under identical analysis parameters. Representative regions of colonic mucosa were selected as regions of interest (ROIs), excluding tissue folds, necrosis, luminal secretions, obvious nonspecific background staining, and edge artifacts. CADM1 and CD11c were quantified as the percentage of positive area (%), whereas p-STAT3, which was primarily nuclear, was quantified as the proportion of positive nuclei (%). All samples were analyzed using consistent thresholds and detection parameters to ensure comparability and reproducibility of the results.

ROC curve analysis

Receiver operating characteristic (ROC) curves were used to evaluate the exploratory discriminatory performance of CADM1, p-STAT3, CD11c, and their combined model. Analyses were performed separately for distinguishing UC patients from controls and for identifying severe UC versus mild-to-moderate UC. In the severe UC analysis, mild and moderate UC patients were combined as a single group (mild-to-moderate UC), with severe UC set as the positive outcome.

GEO database analysis

To further validate the expression patterns of CADM1 and inflammation-related genes in UC, two independent UC transcriptomic datasets (GSE87466 and GSE75214) were obtained from the GEO database. Based on the sample information of each dataset, UC and control groups were defined using the GEO2R online analysis tool, and the differential expression results generated by GEO2R were retrieved. For each gene, the log2 fold change (log2FC) and adjusted P value between UC and control groups were extracted, including CADM1, STAT3, SOCS3, IL6, and TNF. In addition, the expression distributions of these genes in UC and control groups were plotted using the sample expression data provided by GEO2R.

Statistical analysis

Quantitative analysis of images was performed using QuPath software. Statistical analyses were conducted using IBM SPSS Statistics 27 and GraphPad Prism 10.6. Continuous or ordinal variables are presented as median (interquartile range, IQR), and categorical variables are expressed as number (percentage). Comparisons of continuous variables among four groups were performed using the Kruskal–Wallis test, followed by Dunn's post hoc test for multiple comparisons. Comparisons between two groups were performed using the Mann–Whitney U test. Categorical variables were compared using the χ^2 test or Fisher's exact test. Correlations were evaluated using Spearman's rank correlation analysis. All tests were two-sided, and a P value < 0.05 was considered statistically significant.

Results

Baseline characteristics of study participants

A total of 108 participants were included in this study, comprising 13 controls, 34 patients with mild UC, 32 with moderate UC, and 29 with severe UC (Fig. 1). No significant differences were observed in age ($p = 0.07$) or sex distribution ($p = 0.216$) among the four groups. Among UC patients, the distribution of Montreal classification disease extent differed significantly across severity groups ($p < 0.001$). NHI scores also differed significantly among the four groups ($p < 0.001$) and increased with disease severity. Laboratory parameters including WBC ($p < 0.001$), Hb ($p = 0.03$), PLT ($p < 0.001$), and ALB ($p < 0.001$) showed significant differences across groups. CRP ($p < 0.001$) and ESR ($p < 0.001$) were significantly

different among UC subgroups. Overall, patients with severe UC exhibited more pronounced inflammatory responses, lower albumin levels, and higher histological inflammation activity (Table 1).

Table 1
Baseline characteristics of the study participants

	Control	Mild UC	Moderate UC	Severe UC	P value
	(n = 13)	(n = 34)	(n = 32)	(n = 29)	
Age	51 (45–53)	47 (43–54)	46 (41–49)	57 (51–60)	0.07
Sex					0.216
Male, n (%)	5.0 (38.5)	18.0 (52.9)	22.0 (68.8)	14.0 (48.3)	
Female, n (%)	8.0 (61.5)	16.0 (47.1)	10.0 (31.3)	15.0 (51.7)	
Disease extent, n (%)					< 0.001
E1	-	10.0 (29.4)	6.0 (18.8)	0 (0.0)	
E2	-	15.0 (44.1)	8.0 (25.0)	2.0 (6.9)	
E3	-	9.0 (26.5)	18.0 (56.3)	27.0 (93.1)	
NHI	0 (0–0)	2 (1–2)	3 (2–3)	3 (3–4)	< 0.001
WBC (×10^9/L)	4.7 (4.7–5.8)	6.4 (5.5–7.2)	6.0 (5.6-7.0)	7.9 (7.4–9.5)	< 0.001
Hb (g/L)	140.0 (135.3–145.0)	134.0 (121.6-137.1)	126.0 (112.5-129.1)	130.0 (121.0-137.0)	0.03
PLT (×10^9/L)	234.0 (197.0-249.2)	243.5 (220.2-266.8)	284.0 (264.6-322.2)	352.0 (299.0-364.6)	< 0.001
ALB (g/L)	43.2 (41.9–44.5)	43.4 (42.2–44.9)	42.2 (41.1–43.8)	36.2 (33.8–37.6)	< 0.001
CRP (mg/L)	-	1.0 (1.2–2.9)	2.5 (2.3–4.8)	30.5 (29.2–64.0)	< 0.001
ESR (mm/60 min)	-	10.0 (10.0-16.2)	17.5 (16.0-25.9)	32.0 (28.8–49.7)	< 0.001

Data are presented as median (interquartile range) for continuous or ordinal variables and n (%) for categorical variables. Comparisons among groups were performed using the Kruskal–Wallis test for continuous or ordinal variables and the chi-square test or Fisher's exact test for categorical variables, as appropriate. Disease extent, CRP, and ESR were compared among UC subgroups only.

Histological and immunohistochemical findings in UC mucosa

H&E staining showed that the control colonic mucosa had an intact structure, regularly arranged glands, and minimal inflammatory cell infiltration. In contrast, UC mucosa showed varying degrees of inflammatory cell infiltration, crypt architectural distortion, and glandular destruction. These histological changes gradually became more severe as endoscopic inflammatory activity increased from mild to severe UC (Fig. 2A–D). NHI further confirmed significant differences among the four groups ($p < 0.0001$). Dunn's multiple comparison test showed that NHI was higher in the mild, moderate, and severe UC groups than in the control group. NHI was also higher in the moderate and severe UC groups than in the mild UC group, whereas no significant difference was observed between the moderate and severe UC groups (Fig. 2E).

Immunohistochemistry showed that CADM1, p-STAT3, and CD11c expression was generally higher in UC mucosa than in controls and increased to varying degrees with endoscopic activity. CADM1 expression was more evident in inflammatory active areas and inflammation-related cellular components in UC mucosa (Fig. 3A–D). p-STAT3 was mainly detected as nuclear staining and was distributed in lamina propria inflammatory cells and some epithelial cells (Fig. 4A–D). CD11c-positive signals were mainly located in areas of inflammatory cell infiltration in the lamina propria (Fig. 5A–D). Quantitative analysis showed significant differences in CADM1, p-STAT3, and CD11c among the four groups (all $p < 0.001$). Pairwise comparisons showed that CADM1 was significantly higher in the moderate and severe UC groups than in the control and mild UC groups, whereas no significant difference was observed between the moderate and severe UC groups (Fig. 3E). p-STAT3 expression gradually increased with disease activity. The moderate and severe UC groups showed higher p-STAT3 expression than the control group, and the severe UC group showed higher expression than the mild and moderate UC groups (Fig. 4E). CD11c expression was increased in the moderate and severe UC groups compared with the control group. The severe UC group also showed higher CD11c expression than the mild UC group, whereas no significant difference was observed between the moderate and severe UC groups (Fig. 5E).

Correlation analysis between IHC markers and disease activity

Spearman's rank correlation analysis showed that UCEIS score, modified Mayo score, and NHI were generally positively correlated with CADM1, p-STAT3, and CD11c expression to varying degrees (Fig. 6). CADM1 expression was positively correlated with UCEIS score ($r = 0.720$, $p < 0.001$), modified Mayo score ($r = 0.569$, $p < 0.001$), and NHI ($r = 0.542$, $p < 0.001$). CADM1 was also positively correlated with p-STAT3 ($r = 0.632$, $P < 0.001$) and CD11c ($r = 0.604$, $p < 0.001$). p-STAT3 and CD11c expression were also positively correlated with endoscopic, clinical, and histological inflammation scores to varying degrees. Overall, changes in CADM1, p-STAT3, and CD11c expression were consistent with UC disease activity. Among these markers, CADM1 was positively correlated with endoscopic, clinical, and histological inflammatory activity, as well as p-STAT3 and CD11c expression. These findings suggest that CADM1 may be a candidate tissue-related marker reflecting mucosal inflammatory activity in UC.

Discriminatory value of CADM1, p-STAT3, and CD11c for UC and severe UC

To further evaluate the discriminatory performance of CADM1, p-STAT3, and CD11c, ROC curve analysis was performed to assess the ability of these three IHC markers and their combined model to distinguish UC patients from controls and to identify severe UC. In the analysis distinguishing UC patients from controls, CADM1, p-STAT3, and CD11c all showed discriminatory ability. The AUC values were 0.826 (95% CI: 0.726–0.927, $p < 0.0001$), 0.939 (95% CI: 0.876–1.000, $p < 0.0001$), and 0.870 (95% CI: 0.772–0.969, $p < 0.0001$), respectively. The combined model based on CADM1, p-STAT3, and CD11c had an AUC of 0.953 (95% CI: 0.905–1.000, $p < 0.0001$) (Fig. 7A). ROC analysis was further performed with severe UC as the positive outcome. Mild and moderate UC were combined as the non-severe group. CADM1, p-STAT3, and CD11c also showed discriminatory ability for identifying severe UC, with AUC values of 0.808 (95% CI: 0.723–0.894, $p < 0.0001$), 0.881 (95% CI: 0.815–0.948, $p < 0.0001$), and 0.640 (95% CI: 0.519–0.760, $p = 0.03$), respectively. The combined model had an AUC of 0.927 (95% CI: 0.875–0.979, $p < 0.0001$) (Fig. 7B).

GEO validation of CADM1 and inflammation-related markers in UC

Based on two independent GEO cohorts, GSE87466 and GSE75214, we further validated the expression patterns of CADM1 and inflammation-related genes in UC. Differential expression analysis showed that CADM1 was significantly upregulated in UC tissues in both datasets (GSE87466: log2FC = 1.8077, adjusted P value = 2.20×10^{-13}; GSE75214: log2FC = 0.6733, adjusted P value = 7.72×10^{-7}). STAT3, SOCS3, IL6, and TNF also showed a consistent upregulation trend in both cohorts (Fig. 8A). Further expression distribution analysis showed that the expression levels of CADM1, STAT3, SOCS3, IL6, and TNF were higher in the UC group than in the control group in both GSE87466 and GSE75214, with statistically significant differences (Fig. 8B). These findings from public transcriptomic data support the abnormal upregulation of CADM1 and inflammation-related molecules in UC mucosa.

Discussion

This study systematically analyzed CADM1 protein expression in colonic mucosal biopsy tissues from patients with UC and examined its associations with disease activity, p-STAT3 activation, and CD11c-positive cell infiltration. CADM1 expression was higher in UC mucosa than in controls and generally increased with endoscopic activity. CADM1 expression was positively correlated with UCEIS score, modified Mayo score, and NHI. It was also positively correlated with p-STAT3 expression and CD11c-positive cell infiltration. ROC analysis suggested that CADM1, p-STAT3, CD11c, and their combined model had exploratory discriminatory ability for distinguishing UC from controls and severe UC from mild-to-moderate UC. Two independent GEO transcriptomic cohorts also showed upregulation of CADM1 and inflammation-related genes, including STAT3, SOCS3, IL6, and TNF, in UC tissues. These findings

suggest that CADM1 is closely associated with mucosal inflammatory activity and local immune cell infiltration in UC.

The treatment goals for UC have gradually shifted from symptom control to inflammation control. In this context, endoscopic and histological assessments have become increasingly important for disease monitoring, treatment evaluation, and prognostic assessment(23). Clinical symptoms do not fully reflect the mucosal inflammatory burden. In contrast, endoscopic and histological scores assess disease activity from the perspectives of mucosal injury and microscopic inflammation, respectively(24). Previous studies have shown that persistent histological inflammation is closely associated with UC relapse, treatment escalation, and adverse outcomes. Even when clinical symptoms or endoscopic findings improve, residual histological inflammation may still indicate an increased risk of subsequent relapse(25, 26). Persistent histological inflammation is closely associated with UC relapse, treatment escalation, and adverse outcomes. Even when clinical symptoms or endoscopic findings improve, residual histological inflammation may still indicate an increased risk of subsequent relapse. Therefore, the observed increase in CADM1 expression with worsening disease activity may reflect not only local staining intensity but also an increased mucosal inflammatory burden. Compared with peripheral blood inflammatory markers, tissue CADM1 expression may more closely reflect local mucosal pathology and provide a molecular-level complement to conventional scoring systems.

CADM1, a member of the immunoglobulin superfamily of cell adhesion molecules, plays multiple roles, including maintaining intercellular adhesion, stabilizing epithelial structure, and modulating immune cell interactions(27, 28). CADM1 can interact with CRTAM and participate in immune responses involving natural killer cells and CD8 + T cells, suggesting that it is not only a structural adhesion molecule but may also be involved in local immune responses(18, 29). A recent study in IBD suggested that CADM1 is upregulated in inflamed intestinal tissues and may be related to myeloid cell-mediated immune responses(20). In this context, the present study further evaluated CADM1 expression in conventional FFPE colonic mucosal biopsy tissues. We found that CADM1 expression was increased in UC mucosa and was positively correlated with both p-STAT3 and CD11c. These findings suggest that changes in CADM1 expression may be associated with local inflammatory signaling activation and myeloid inflammatory cell infiltration.

The IL-6/JAK/STAT3 signaling axis is a key pathway in mucosal inflammation in UC and is involved in immune cell activation, epithelial stress responses, mucosal repair, and amplification of inflammatory signaling(12). After phosphorylation at Tyr705, STAT3 enters the nucleus and regulates the transcription of inflammation-related genes. Therefore, p-STAT3 can serve as a histological marker reflecting the activation status of the STAT3 signaling pathway(30, 31). Recent studies in IBD have also suggested that CADM1 may be involved in STAT3-related inflammatory signaling. In the present study, p-STAT3 expression was increased in UC mucosa and positively correlated with CADM1; GEO analyses further showed upregulation of STAT3, SOCS3, IL6, and TNF in UC tissues. These findings indicate that elevated CADM1 may be associated with enhanced STAT3-related inflammatory signaling(20).

In this study, CD11c was mainly used as an auxiliary marker of myeloid inflammatory cell infiltration. CD11c-positive cells were mainly located in areas of inflammatory cell infiltration in the lamina propria and were positively correlated with CADM1 expression. This suggests that high CADM1 expression may be accompanied by local accumulation of myeloid inflammatory cells in UC mucosa(14, 32). This finding further supports CADM1 as a potential indicator of local myeloid inflammatory cell infiltration and immune microenvironment changes in UC mucosa.

Two independent GEO transcriptomic cohorts further supported the findings of this study. Both GSE87466 and GSE75214 showed upregulation of CADM1 in UC mucosal tissues, accompanied by increased expression of inflammation-related genes including STAT3, SOCS3, IL6, and TNF(33, 34). This result was consistent with our IHC findings, suggesting that increased CADM1 expression may be associated with mucosal inflammation and inflammatory signaling activation in UC.

This study has several limitations. First, this was a single-center retrospective study with a relatively limited sample size. The stability of the findings should be further validated in larger multicenter cohorts. Second, this study was mainly based on conventional FFPE colonic mucosal biopsy tissues, which reflect the type of samples commonly available in clinical pathology practice. However, dynamic samples before and after treatment and long-term follow-up outcomes were not included. Therefore, the value of CADM1 in predicting treatment response or prognosis requires further evaluation. Third, IHC and digital pathology quantification allowed us to assess the relationships among CADM1, p-STAT3, CD11c, and inflammatory activity at the tissue level. However, the precise cellular source of CADM1 and its spatial relationship with different immune cell subsets remain to be clarified by multiplex immunofluorescence, single-cell analysis, or spatial omics approaches. Finally, the ROC analysis in this study was exploratory, and the clinical utility of the combined model requires validation in independent cohorts. Future studies based on clinical biopsy samples, together with functional experiments and longitudinal follow-up, are needed to further evaluate CADM1 as a tissue marker associated with mucosal inflammatory activity in UC.

Conclusions

In summary, CADM1 expression was elevated in UC colonic mucosa and was closely associated with endoscopic, clinical, and histological inflammation, as well as p-STAT3 activation and CD11c-positive cell infiltration. Public transcriptomic data further supported the upregulation of CADM1 and inflammation-related genes in UC. These findings suggest that CADM1 may serve as a tissue biomarker reflecting mucosal inflammatory activity and local immune microenvironment changes, providing a basis for further CADM1-related studies using clinical biopsy samples.

Abbreviations

ALB
Albumin

AUC
Area under the curve
CADM1
Cell adhesion molecule 1
CI
Confidence interval
CRP
C-reactive protein
DAB
3,3'-diaminobenzidine
ESR
Erythrocyte sedimentation rate
FFPE
Formalin-fixed paraffin-embedded
GEO
Gene Expression Omnibus
H&E
Hematoxylin and eosin
Hb
Hemoglobin
IBD
Inflammatory bowel disease
IHC
Immunohistochemistry
IL6
Interleukin 6
NHI
Nancy histological index
PLT
Platelet count
ROC
Receiver operating characteristic
SOCS3
Suppressor of cytokine signaling 3
STAT3
Signal transducer and activator of transcription 3
TNF
Tumor necrosis factor
UC
Ulcerative colitis

UCEIS
Ulcerative Colitis Endoscopic Index of Severity
WBC
White blood cell count.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Xiangyang No.1 People's Hospital (approval number: 2025KY026). The requirement for written informed consent was waived by the ethics committee because this retrospective study used archived FFPE tissue samples and anonymized clinical data. All procedures were performed in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Author Contribution

ZL and DW conceptualized and designed the study. HM collected the tissue samples. RW and JL collected the clinical data. JT and HM performed the pathological evaluation. ZL and DW performed the immunohistochemistry experiments. ZL conducted the data analysis. ZL wrote the original draft. DW contributed to experimental work and data interpretation. CX supervised the study and critically revised the manuscript. All authors reviewed and edited the manuscript. All authors read and approved the final version of the manuscript.

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Not applicable.

Availability of data and materials

The datasets used or analyzed during the current study are available from the corresponding author on reasonable request. Publicly available transcriptomic datasets analyzed in this study are available in the Gene Expression Omnibus repository under accession numbers GSE87466 and GSE75214.

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Figures

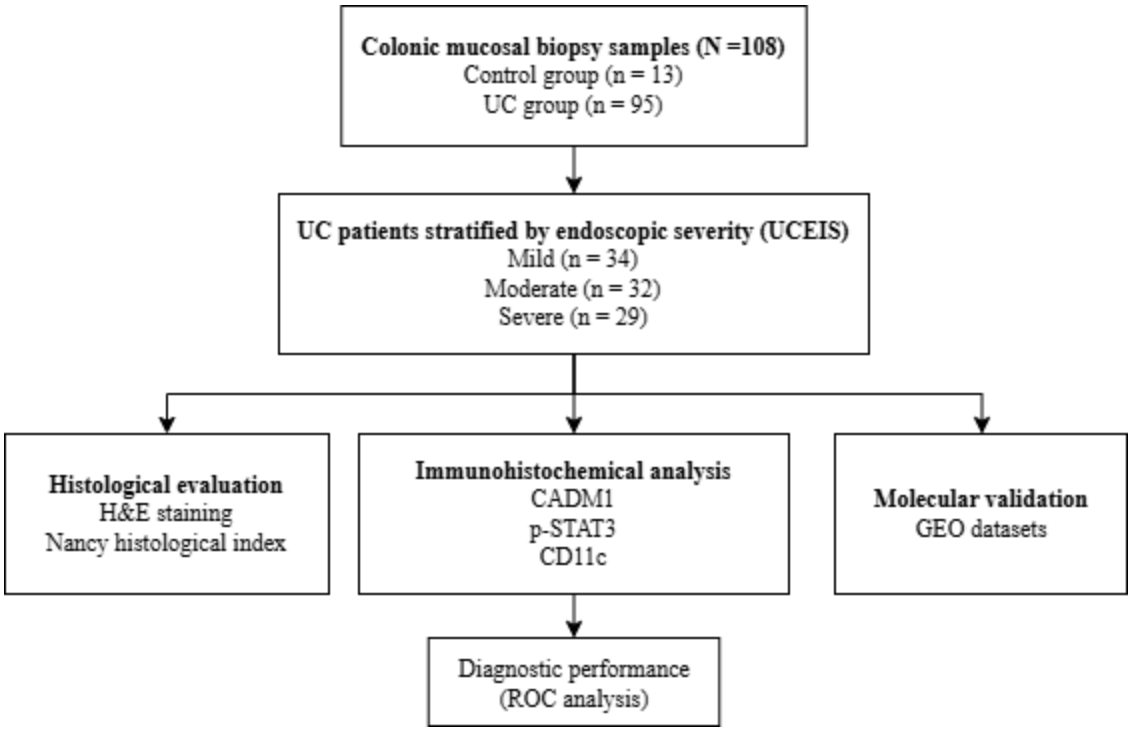


Figure 1

Overall workflow of the study.

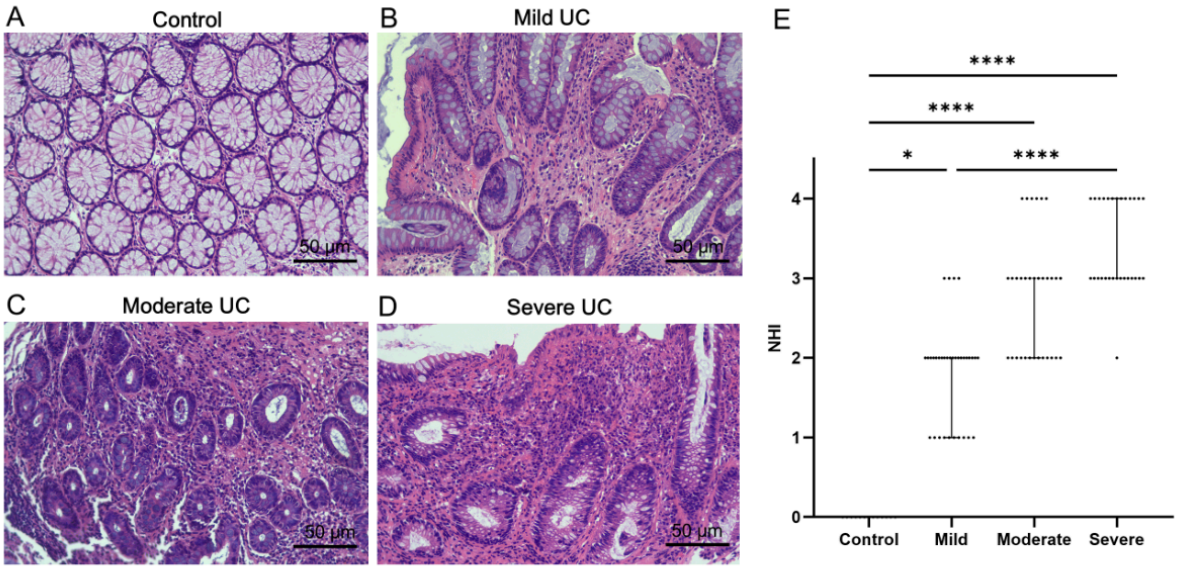


Figure 2

Histological findings and NHI comparison in colonic mucosa.

(A–D) Representative H&E staining images of colonic mucosa from the control, mild UC, moderate UC, and severe UC groups. Scale bar = 50 μm. (E) Comparison of NHI among the four groups. Data are shown as individual values with median and interquartile range. Comparisons were performed using the Kruskal–Wallis test followed by Dunn's multiple comparison test. *P < 0.05, ****P < 0.0001.

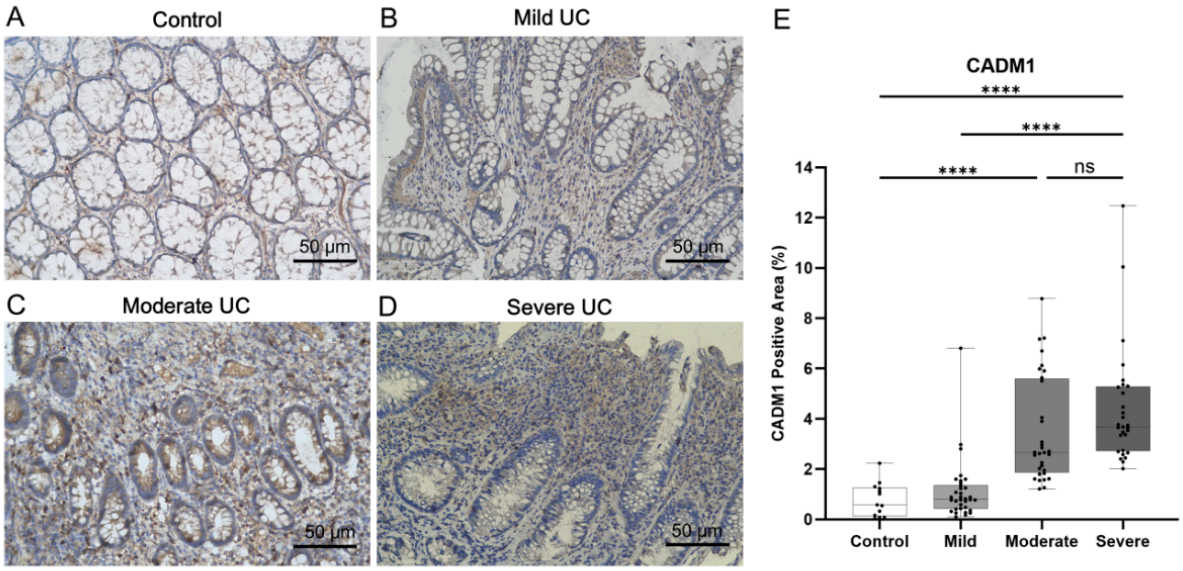


Figure 2. Representative CADM1 immunohistochemical staining and quantitative analysis.
(A–D) Representative immunohistochemical staining of CADM1 in colonic tissues from the control, mild UC, moderate UC, and severe UC groups. Scale bar = 50 μm.
(E) Quantification of CADM1 positive area among the four groups. Data are presented as median with interquartile range. Comparisons were performed using the Kruskal–Wallis test followed by Dunn's post hoc test. **P < 0.01, ***P < 0.001, ****P < 0.0001.

Figure 3

CADM1 immunohistochemical staining and quantitative analysis in colonic mucosa.

(A–D) Representative immunohistochemical staining of CADM1 in colonic mucosa from the control, mild UC, moderate UC, and severe UC groups. Scale bar = 50 μm. (E) Quantification of CADM1-positive area among the four groups. Data are shown as individual values with median and interquartile range. Comparisons were performed using the Kruskal–Wallis test followed by Dunn's multiple comparison test. ****P < 0.0001.

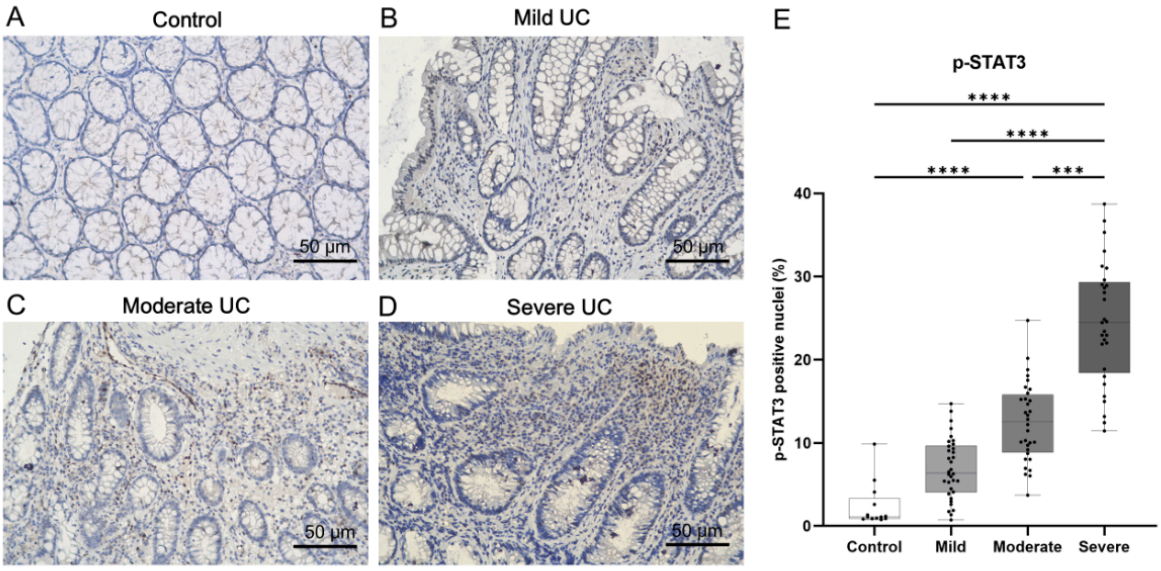


Figure 2. Representative CADM1 immunohistochemical staining and quantitative analysis.
(A–D) Representative immunohistochemical staining of CADM1 in colonic tissues from the control, mild UC, moderate UC, and severe UC groups. Scale bar = 50 μm.
(E) Quantification of CADM1 positive area among the four groups. Data are presented as median with interquartile range. Comparisons were performed using the Kruskal–Wallis test followed by Dunn's post hoc test. **P < 0.01, ***P < 0.001, ****P < 0.0001.

Figure 4

p-STAT3 immunohistochemical staining and quantitative analysis in colonic mucosa.

(A–D) Representative immunohistochemical staining of p-STAT3 in colonic mucosa from the control, mild UC, moderate UC, and severe UC groups. Scale bar = 50 μm. (E) Quantification of p-STAT3-positive nuclei among the four groups. Data are shown as individual values with median and interquartile range. Comparisons were performed using the Kruskal–Wallis test followed by Dunn's multiple comparison test. *P < 0.05, ***P < 0.001, ****P < 0.0001.

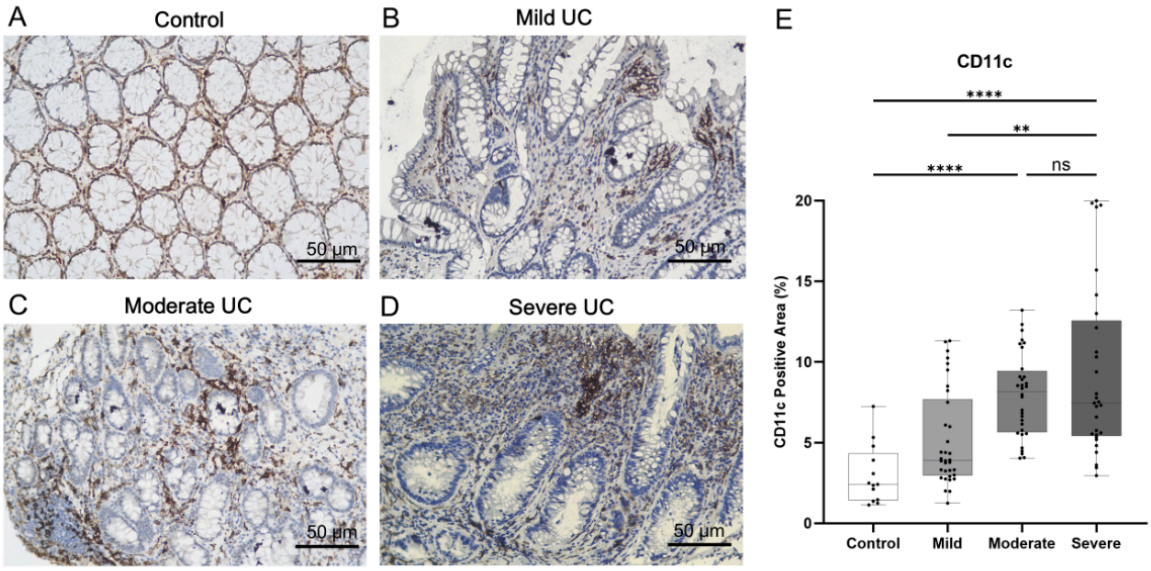


Figure 5

CD11c immunohistochemical staining and quantitative analysis in colonic mucosa.

(A–D) Representative immunohistochemical staining of CD11c in colonic mucosa from the control, mild UC, moderate UC, and severe UC groups. Scale bar = 50 μm. (E) Quantification of CD11c-positive area among the four groups. Data are shown as individual values with median and interquartile range. Comparisons were performed using the Kruskal–Wallis test followed by Dunn's multiple comparison test. **P < 0.01, ****P < 0.0001

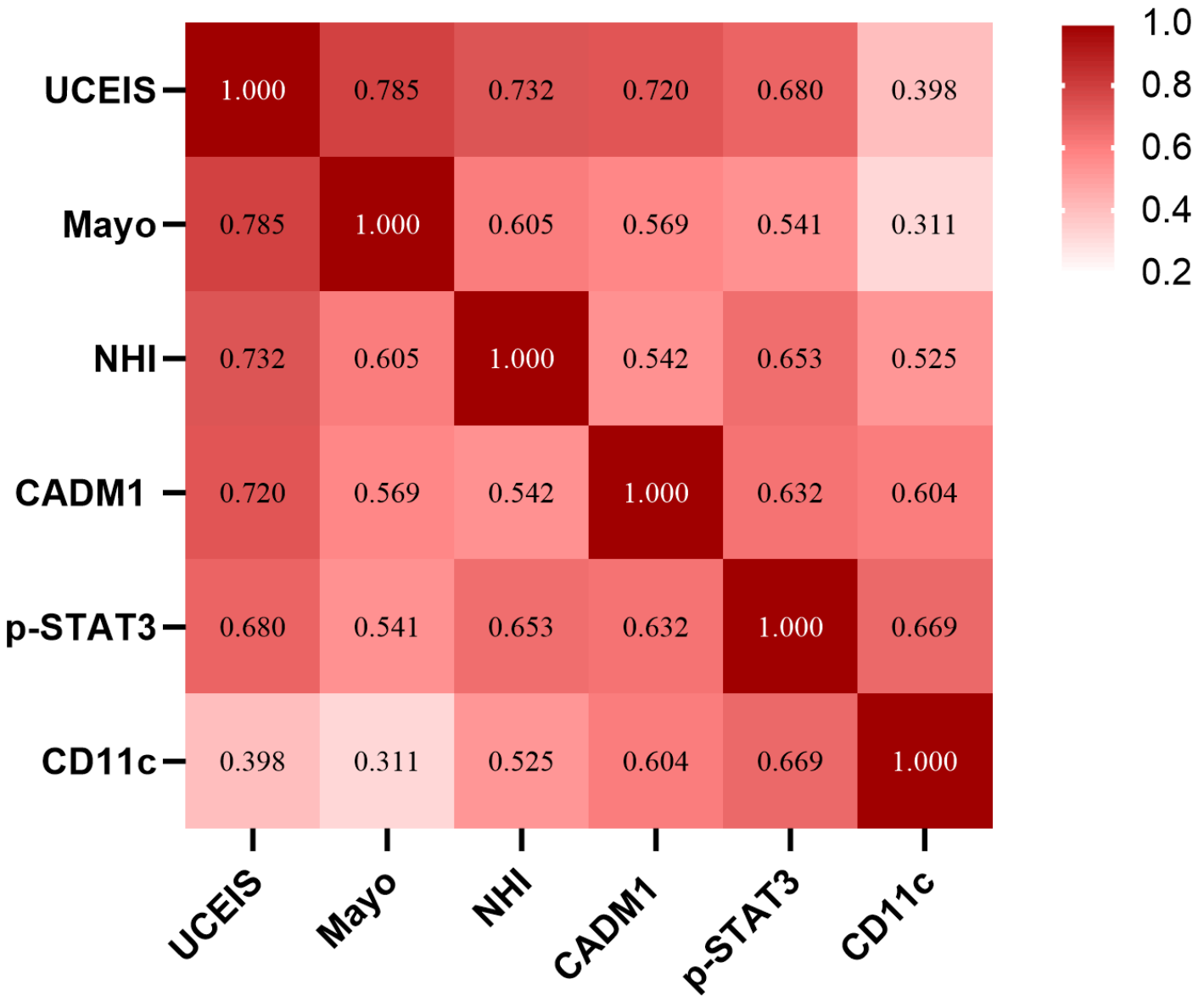


Figure 6

Correlation heatmap of disease activity scores and IHC markers.

Spearman's rank correlation analysis was performed to evaluate the associations among UCEIS score, modified Mayo score, NHI, CADM1, p-STAT3, and CD11c. The heatmap shows Spearman correlation coefficients. Color intensity indicates the strength of correlation. ***P < 0.001.

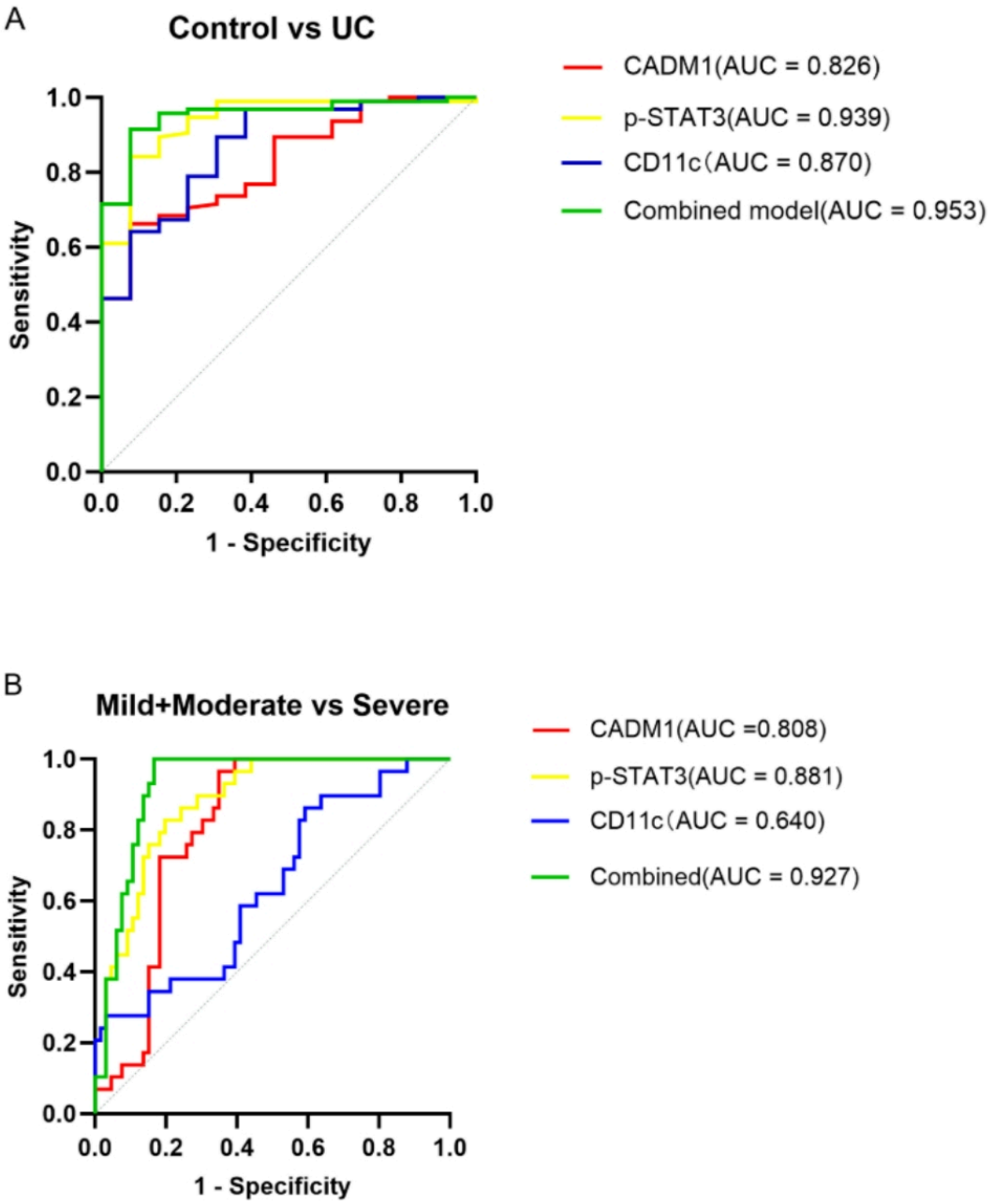


Figure 7

ROC analysis of CADM1, p-STAT3, CD11c, and the combined model.

(A) ROC curves for distinguishing UC patients from controls. (B) ROC curves for identifying severe UC from mild-to-moderate UC. The combined model was constructed using binary logistic regression with

CADM1, p-STAT3, and CD11c as predictors. AUC, area under the curve; ROC, receiver operating characteristic.

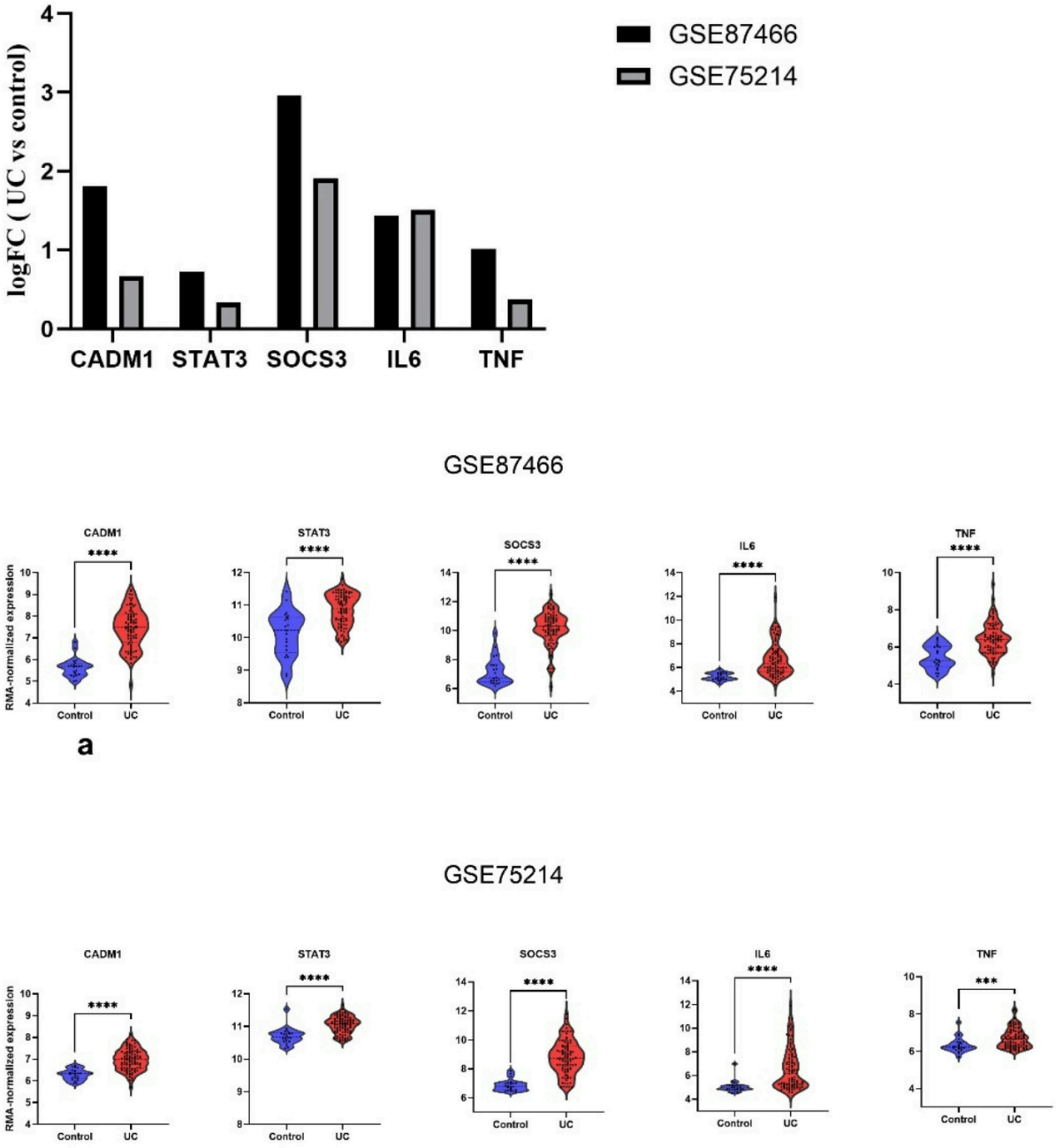


Figure 8

GEO-based validation of CADM1 and inflammation-related gene expression in UC.

(A) Summary of log2FC values for CADM1, STAT3, SOCS3, IL6, and TNF in GSE87466 and GSE75214. (B) Expression distribution of CADM1, STAT3, SOCS3, IL6, and TNF in the control and UC groups. ***P < 0.001, ****P < 0.0001.