NIU Journal of Health Sciences Copyright©2026
Nexus International University ISSN: 3136-6449; 12(3) 135-146

Growth Differentiation Factor-15, Extracellular NAMPT and Interleukin-22 in Ulcerative Colitis: Associations with Disease Activity and Intestinal Barrier Integrity: A Single-Centre Case–Control Study at Al-Kadhimiya Teaching Hospital, Baghdad, Iraq

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Abstract

Background: Ulcerative colitis (UC) is a relapsing–remitting inflammatory disorder of the colonic mucosa in which loss of epithelial barrier integrity, mitochondrial and metabolic stress, and dysregulated mucosal cytokine networks act together to sustain inflammation. Growth differentiation factor-15 (GDF-15), extracellular nicotinamide phosphoribosyltransferase (eNAMPT/visfatin) and interleukin-22 (IL-22) each sit at the interface between cellular stress, innate immune activation and epithelial repair, but they have not previously been assessed together in an Iraqi UC cohort alongside a panel of circulating barrier markers.
Objectives: To measure serum GDF-15, eNAMPT and IL-22 in patients with UC and in healthy controls; to relate them to clinical, endoscopic and biochemical indices of disease activity; to examine their relationship with circulating and urinary markers of intestinal barrier failure; and to evaluate their diagnostic performance individually and as a combined panel.
Patients and Methods: This case–control study was conducted at Al-Kadhimiya Teaching Hospital, Baghdad, Iraq, between 1 October 2024 and 1 June 2025. Ninety adults with endoscopically and histologically confirmed UC and forty-five age-, sex- and body-mass-index-matched healthy controls were enrolled. Disease extent was classified by the Montreal system and activity by the total Mayo score. Serum GDF-15, eNAMPT, IL-22, zonulin, intestinal fatty acid-binding protein (I-FABP), lipopolysaccharide (LPS) and LPS-binding protein (LBP), together with urinary claudin-3, were quantified by enzyme-linked immunosorbent assay. Fecal calprotectin, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), haemoglobin and albumin were measured by routine laboratory methods. Group comparisons, Spearman correlations, receiver operating characteristic (ROC) analysis and multivariable logistic regression were applied.
Results: All three index biomarkers were markedly higher in patients than controls: GDF-15 1186 (742–1890) versus 468 (352–610) pg/mL, eNAMPT 6.84 ± 2.31 versus 2.47 ± 0.86 ng/mL and IL-22 47.6 (28.3–82.1) versus 14.2 (9.8–20.5) pg/mL (all $P < 0.001$), as were every barrier marker examined. GDF-15 and eNAMPT rose stepwise across remission, mild, moderate and severe disease, whereas IL-22 peaked in moderate disease (72.8 pg/mL) and fell in severe disease (55.1 pg/mL). GDF-15 and eNAMPT correlated strongly with the total Mayo score ($r = 0.72$ and $r = 0.68$), the Mayo endoscopic subscore, fecal calprotectin and CRP, and moderately with zonulin, I-FABP and LPS; IL-22 showed consistently weaker correlations with barrier markers. For discriminating UC from controls the area under the curve (AUC) was 0.91 for GDF-15, 0.93 for eNAMPT and 0.87 for IL-22, rising to 0.97 for the three-marker panel; for active versus quiescent disease the panel achieved an AUC of 0.93. After adjustment for age, sex, disease extent and therapy, GDF-15 (adjusted odds ratio [aOR] 2.68 per 500 pg/mL), eNAMPT (aOR 1.52 per 1 ng/mL) and zonulin (aOR 1.38 per 10 ng/mL) remained independently associated with active disease, while IL-22 lost significance (aOR 1.14, $P = 0.28$).
Conclusions: GDF-15 and eNAMPT behave as activity-tracking, barrier-linked biomarkers in Iraqi patients with UC and retain independent associations with active disease after multivariable adjustment, whereas IL-22 behaves as a non-linear, reparative cytokine whose serum concentration peaks at intermediate disease severity. A three-marker panel substantially outperforms any single analyte and merits prospective validation as a non-invasive adjunct to endoscopy.

Keywords: Ulcerative colitis; growth differentiation factor-15; nicotinamide phosphoribosyltransferase; visfatin; interleukin-22; intestinal permeability; zonulin; Iraq.

1. Introduction

Ulcerative colitis (UC) is a chronic immune-mediated disorder characterised by continuous mucosal inflammation that begins in the rectum and extends proximally for a variable distance along the colon. Its global footprint has changed substantially over the past two decades: incidence has plateaued in long-industrialised regions while rising steeply in newly industrialised countries, where hospitalisation rates for inflammatory bowel disease (IBD) continue to climb and place a growing burden on health systems that were not configured for chronic immune-mediated disease [1,2]. Hospital-based series from Iraq have documented a comparable pattern of increasing recognition, with UC consistently outnumbering Crohn's disease and affecting predominantly young adults in their third and fourth decades [3,29,30].

Three pathogenic processes dominate contemporary models of UC. The first is failure of the epithelial barrier, in which loss of tight-junction proteins and accelerated enterocyte turnover permit luminal antigens and bacterial products to reach the lamina propria. The second is innate immune activation driven by endogenous danger signals released from stressed or dying cells. The third is a dysregulated cytokine environment in which pro-inflammatory and reparative mediators are produced simultaneously but in a spatial and temporal pattern that fails to resolve the lesion [7]. Iraqi investigators have contributed to the cytokine component of this picture, reporting elevated circulating IL-17A, IL-23, IL-6 and calprotectin in local UC populations [4,5,6,31]; what has been lacking is a parallel assessment of the stress-responsive and barrier-directed arms of the same pathway.

Growth differentiation factor-15 (GDF-15), also known as macrophage inhibitory cytokine-1, is a distant member of the transforming growth factor-β superfamily whose transcription is induced by mitochondrial stress, the integrated stress response, hypoxia and inflammation. Once secreted it signals centrally through the hindbrain receptor GFRAL–RET to suppress appetite, and peripherally it exerts complex, context-dependent effects on inflammation and tissue remodelling [8,9]. Circulating GDF-15 is elevated in IBD and tracks disease severity, anaemia and conventional inflammatory indices [10–12,14]. More recently, GDF-15 has been shown to act directly on colonic epithelium, reducing zonula occludens-1 and claudin-1 expression and increasing permeability in organoid and monolayer models, a finding that reframes it from a passive severity marker into a plausible effector of barrier failure [13].

Nicotinamide phosphoribosyltransferase (NAMPT) is the rate-limiting enzyme of the salvage pathway for nicotinamide adenine dinucleotide. Its extracellular form (eNAMPT, historically termed visfatin or pre-B-cell colony-enhancing factor) behaves less like a metabolic enzyme than like a damage-associated molecular pattern: it is a Toll-like receptor 4 (TLR4) ligand that drives nuclear factor-κB-dependent cytokine production in a range of inflammatory states [20,21]. In IBD, NAMPT is over-expressed in both inflamed and quiescent bowel and over-secreted into the circulation, where it mirrors clinical and endoscopic activity, the severity of the inflammatory response and tissue hypoxia [15]. Serum visfatin has been proposed as a non-invasive diagnostic marker of active IBD and as a predictor of disease extent in UC [16], and adipokine profiling studies have repeatedly placed it among the few mediators that are consistently raised in both UC and Crohn's disease [17–19].

Interleukin-22 (IL-22) occupies a different position in the same network. Produced by group 3 innate lymphoid cells, Th17 and Th22 cells, it acts exclusively on non-haematopoietic cells bearing the IL-22RA1 receptor, which in the gut means the epithelium. Through signal transducer and activator of transcription 3, IL-22 induces antimicrobial peptides, mucins and proliferative and anti-apoptotic programmes, and is required for Paneth-cell formation in human small-intestinal organoids [22,23,25]. Yet the same cytokine also drives CXC-chemokine expression and neutrophil recruitment into the colonic mucosa, and enrichment of IL-22-regulated transcripts in UC biopsies has been associated with resistance to ustekinumab [24]. IL-22 is therefore expected to behave non-monotonically across the activity spectrum, which makes it an informative counterweight to the stress-derived markers in any combined panel.

Circulating and urinary indicators of barrier failure provide the link between these mediators and mucosal physiology. Zonulin reflects regulated opening of tight junctions, I-FABP is released from damaged enterocytes, LPS and LBP index translocation of bacterial products, and urinary claudin-3 reflects shedding of tight-junction protein into the circulation and its subsequent renal clearance. These markers have been applied in IBD, in primary sclerosing cholangitis and in functional bowel disease, with broadly concordant results [26–28].

No study to date has measured GDF-15, eNAMPT and IL-22 simultaneously in UC alongside a comprehensive barrier panel, and none has done so in an Iraqi population. The present study was therefore designed with four objectives: to compare these three mediators between UC patients and healthy controls; to describe their behaviour across clinical activity strata; to quantify their association with endoscopic, faecal, serological and barrier indices; and to determine, by ROC analysis and multivariable modelling, whether they add independent diagnostic information beyond established markers.

2. Patients and Methods

2.1 Study Design and Setting

This hospital-based, observational case–control study was carried out in the Gastroenterology Unit and the clinical laboratories of Al-Kadhimiya Teaching Hospital, Baghdad, Iraq. Recruitment and sample collection ran from 1 October 2024 to 1 June 2025, a continuous eight-month period during which all eligible attendees were approached consecutively in order to minimise selection bias.

2.2 Ethical Approval and Consent

The protocol was reviewed and approved by the institutional scientific and ethics committee of Al-Kadhimiya Teaching Hospital on 1 September 2024, before any participant was enrolled; no approval reference number was assigned by the committee. The study was conducted in accordance with the Declaration of Helsinki and with the research-governance requirements of the Iraqi Ministry of Health. Written informed consent was obtained from every patient and every control after a verbal and written explanation of the purpose of the study, the nature of the samples required, the absence of any additional invasive procedure performed solely for research, and the participant's right to withdraw at any point without consequence for their clinical care. All data were pseudonymised at the point of collection and stored on a password-protected device accessible only to the investigators.

2.3 Participants

Ninety adults with UC were enrolled. Eligibility required a diagnosis established at least three months earlier on the basis of compatible clinical features, endoscopic findings of continuous mucosal inflammation extending proximally from the rectum, and histopathological confirmation on colonic biopsy, in line with accepted international diagnostic criteria. Patients aged 18 years or older of either sex were eligible irrespective of disease extent, activity or current therapy.

Exclusion criteria were applied to limit confounding of the index biomarkers, each of which can be elevated by non-intestinal pathology. Patients were excluded if they had Crohn's disease or unclassified IBD; coexisting coeliac disease or another enteropathy; an enteric infection, including Clostridioides difficile, within the preceding four weeks; malignancy of any site; congestive heart failure, ischaemic heart disease or chronic kidney disease (estimated glomerular filtration rate below 60 mL/min/1.73 m²); chronic liver disease; diabetes mellitus; a body mass index of 35 kg/m² or above; pregnancy or lactation; current metformin therapy, which independently raises circulating GDF-15; or colectomy or any abdominal surgery within six months.

Forty-five healthy volunteers, frequency-matched to the patient group for age, sex and body mass index, were recruited from hospital staff and from accompanying relatives of patients attending unrelated clinics. Controls had no gastrointestinal symptoms, no personal or first-degree family history of IBD, normal routine haematological and biochemical indices, and none of the exclusion criteria listed above.

2.4 Clinical Assessment and Disease Classification

Demographic data, smoking status, disease duration and current medication were recorded on a structured proforma. Disease extent was classified according to the Montreal system as proctitis (E1), left-sided colitis (E2) or extensive colitis (E3). Disease activity was quantified with the total Mayo score, which combines stool frequency, rectal bleeding, the endoscopic subscore and the physician's global assessment, each rated 0 to 3 for a maximum of 12. For stratified analysis, patients were grouped as being in remission (0–2), or as having mild (3–5), moderate (6–9) or

severe (10–12) disease. Endoscopy was performed as part of routine clinical care by a consultant gastroenterologist blinded to the biomarker results, and the Mayo endoscopic subscore was recorded separately for correlation analysis. Active disease was defined for the purposes of regression modelling as a total Mayo score of 3 or more.

2.5 Sample Collection and Handling

Venous blood (8 mL) was drawn after an overnight fast of at least ten hours, before any endoscopic bowel preparation, and collected into plain gel tubes and EDTA tubes. Serum was separated by centrifugation at 3000 × g for ten minutes within one hour of venepuncture, divided into single-use aliquots and stored at −80 °C until assay; repeated freeze–thaw cycles were avoided. A spot mid-stream urine sample was collected at the same visit, centrifuged to remove cellular debris and stored under identical conditions. A single stool sample was collected within 72 hours of venepuncture for calprotectin measurement.

2.6 Laboratory Measurements

Commercial sandwich enzyme-linked immunosorbent assay kits from SunLong Biotech Co., Ltd. (Hangzhou, China) were used to quantify serum GDF-15 (Cat. No. SL2293Hu), eNAMPT/visfatin (Cat. No. SL1825Hu), IL-22 (Cat. No. SL0988Hu), zonulin (Cat. No. SL2712Hu), intestinal fatty acid-binding protein (I-FABP; Cat. No. SL1010Hu) and lipopolysaccharide-binding protein (LBP; Cat. No. SL1078Hu), as well as urinary claudin-3 (Cat. No. SL3296Hu), according to the manufacturer's instructions without modification. Serum LPS was quantified by a chromogenic Limulus amoebocyte lysate assay using endotoxin-free consumables throughout. All assays were performed in duplicate in a single batch by an operator blinded to group allocation; samples falling above the upper limit of linearity were diluted and re-assayed. According to the manufacturer's specifications, the intra-assay and inter-assay coefficients of variation were below 8% and 10%, respectively. Fecal calprotectin was measured by quantitative ELISA on an extracted stool aliquot. C-reactive protein was determined by immunoturbidimetry, the erythrocyte sedimentation rate by the Westergren method, and haemoglobin and serum albumin on automated haematology and chemistry analysers under standard internal and external quality control.

2.7 Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics, version 26.0 (IBM Corp., Armonk, NY, USA). Distributional normality was assessed with the Shapiro–Wilk test and inspection of histograms and Q–Q plots. Normally distributed variables are presented as mean ± standard deviation and compared with the independent-samples t test; skewed variables are presented as median (interquartile range) and compared with the Mann–Whitney U test. Categorical variables are presented as counts and percentages and compared with the χ^2 or Fisher exact test. Comparisons across the four activity strata used one-way analysis of variance or the Kruskal–Wallis test as appropriate, with post hoc pairwise testing adjusted for multiple comparisons. Associations between continuous variables were examined by Spearman rank correlation, the coefficients being interpreted as weak (below 0.30), moderate (0.30–0.59) or strong (0.60 or above). Diagnostic performance was assessed by ROC analysis; optimal cut-offs were selected by the Youden index, and the combined three-marker model was derived from the predicted probabilities of a logistic regression containing GDF-15, eNAMPT and IL-22. Variables associated with active disease at $P < 0.10$ in univariable analysis were entered into a multivariable logistic regression adjusted a priori for age, sex, disease extent and biologic therapy; results are reported as odds ratios with 95% confidence intervals. A two-sided P value of less than 0.05 was considered statistically significant. With 90 patients and 45 controls, the study had greater than 90% power to detect a standardised between-group difference of 0.6 at $\alpha = 0.05$.

3. Results

3.1 Characteristics of the Study Population

The two groups were well matched. Mean age was 38.6 ± 11.4 years in patients and 37.2 ± 10.8 years in controls ($P = 0.49$), the male-to-female ratio was identical in both groups at 53.3% to 46.7% ($P = 1.00$), and mean body mass index was 24.8 ± 3.6 against 25.3 ± 3.2 kg/m² ($P = 0.42$). Current smoking was reported by 15.6% of patients and 17.8% of controls ($P = 0.74$). Median disease duration was 4.5 years (interquartile range 2.0–8.0). Left-sided colitis was the commonest Montreal category (43.3%), followed by extensive colitis (36.7%) and proctitis (20.0%). The median total

Mayo score was 6 (3–9). Almost half the cohort (45.6%) was receiving 5-aminosalicylates alone, with 24.4% on thiopurines, 18.9% on corticosteroids and 11.1% on anti-tumour necrosis factor or anti-integrin therapy.

Routine indices confirmed an inflammatory and nutritionally compromised phenotype in the patient group: haemoglobin and serum albumin were significantly lower, and CRP, ESR and fecal calprotectin significantly higher, than in controls (all $P < 0.001$). The full comparison is shown in Table 1.

Table 1: Demographic and clinical characteristics of patients with ulcerative colitis and healthy controls.

Variable	UC patients (n = 90)	Controls (n = 45)	P value
Age (years), mean ± SD	38.6 ± 11.4	37.2 ± 10.8	0.49
Sex, male/female, n (%)	48/42 (53.3/46.7)	24/21 (53.3/46.7)	1.00
Body mass index (kg/m²)	24.8 ± 3.6	25.3 ± 3.2	0.42
Current smoking, n (%)	14 (15.6)	8 (17.8)	0.74
Disease duration (years), median (IQR)	4.5 (2.0–8.0)	—	—
Montreal extent: E1 proctitis, n (%)	18 (20.0)	—	—
E2 left-sided colitis, n (%)	39 (43.3)	—	—
E3 extensive colitis, n (%)	33 (36.7)	—	—
Total Mayo score, median (IQR)	6 (3–9)	—	—
Current therapy: 5-ASA only, n (%)	41 (45.6)	—	—
Thiopurines, n (%)	22 (24.4)	—	—
Corticosteroids, n (%)	17 (18.9)	—	—
Biologic (anti-TNF / anti-integrin), n (%)	10 (11.1)	—	—
Haemoglobin (g/dL)	11.9 ± 1.8	13.8 ± 1.3	< 0.001
Serum albumin (g/dL)	3.6 ± 0.5	4.3 ± 0.3	< 0.001
CRP (mg/L), median (IQR)	12.4 (4.1–28.6)	1.8 (0.9–3.2)	< 0.001
ESR (mm/h)	28.3 ± 14.2	9.6 ± 4.1	< 0.001
Fecal calprotectin (µg/g), median (IQR)	412 (168–895)	32 (18–49)	< 0.001

5-ASA, 5-aminosalicylic acid; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IQR, interquartile range; SD, standard deviation; TNF, tumour necrosis factor; UC, ulcerative colitis.

3.2 Biomarker and Barrier Profile in Patients Versus Controls

All three index mediators were substantially elevated in UC. Median serum GDF-15 was 1186 (742–1890) pg/mL in patients compared with 468 (352–610) pg/mL in controls, a 2.5-fold difference. Mean eNAMPT was 6.84 ± 2.31 against 2.47 ± 0.86 ng/mL, a 2.8-fold difference, and median IL-22 was 47.6 (28.3–82.1) against 14.2 (9.8–20.5) pg/mL, the largest relative increase at 3.4-fold. Every barrier index moved in the same direction: zonulin and LBP approximately doubled, urinary claudin-3 and I-FABP rose roughly 2.3- to 2.4-fold, and LPS rose 2.7-fold. All comparisons reached $P < 0.001$ (Table 2).

Table 2: Serum GDF-15, eNAMPT and IL-22 and markers of intestinal barrier integrity in patients and controls.

Biomarker	UC patients (n = 90)	Controls (n = 45)	Fold increase	P value
Serum GDF-15 (pg/mL)	1186 (742–1890)	468 (352–610)	2.5	< 0.001
Serum eNAMPT/visfatin (ng/mL)	6.84 ± 2.31	2.47 ± 0.86	2.8	< 0.001
Serum IL-22 (pg/mL)	47.6 (28.3–82.1)	14.2 (9.8–20.5)	3.4	< 0.001
Serum zonulin (ng/mL)	58.4 ± 17.9	29.6 ± 8.2	2.0	< 0.001
I-FABP (pg/mL)	1245 (786–2130)	512 (398–705)	2.4	< 0.001
LPS (EU/mL)	0.84 ± 0.31	0.31 ± 0.12	2.7	< 0.001
LBP (µg/mL)	18.7 ± 6.4	8.9 ± 2.7	2.1	< 0.001
Urinary claudin-3 (ng/mL)	4.92 ± 1.74	2.18 ± 0.69	2.3	< 0.001

Data are mean ± SD or median (interquartile range). eNAMPT, extracellular nicotinamide phosphoribosyltransferase; EU, endotoxin units; GDF-15, growth differentiation factor-15; I-FABP, intestinal fatty acid-binding protein; IL-22, interleukin-22; LBP, lipopolysaccharide-binding protein; LPS, lipopolysaccharide.

3.3 Biomarker behaviour across disease activity strata

Stratification by total Mayo score revealed two distinct patterns. GDF-15, eNAMPT, zonulin, I-FABP, LPS, fecal calprotectin and CRP all increased monotonically from remission to severe disease. GDF-15 rose almost fourfold across the spectrum, from a median of 612 pg/mL in remission to 2310 pg/mL in severe disease, and eNAMPT rose from 4.12 ± 1.20 to 10.4 ± 2.3 ng/mL. The barrier markers followed the same gradient, zonulin more than doubling and I-FABP increasing 3.6-fold between the extremes.

IL-22 behaved differently. It climbed from 24.5 pg/mL in remission through 41.3 pg/mL in mild disease to a maximum of 72.8 (49.2–96.5) pg/mL in moderate disease, then declined to 55.1 (36.4–81.9) pg/mL in severe disease. The overall test across strata remained highly significant ($P < 0.001$), but the trajectory was inverted-U rather than linear (Table 3).

Table 3: Biomarker concentrations stratified by disease activity (total Mayo score).

Biomarker	Remission (0–2) n = 24	Mild (3–5) n = 26	Moderate (6–9) n = 25	Severe (10–12) n = 15	P value
GDF-15 (pg/mL)	612 (480–790)	948 (710–1240)	1465 (1120–1980)	2310 (1740–3050)	< 0.001
eNAMPT (ng/mL)	4.12 ± 1.20	5.86 ± 1.54	7.95 ± 1.88	10.4 ± 2.3	< 0.001
IL-22 (pg/mL)	24.5 (17.8–33.1)	41.3 (29.6–58.4)	72.8 (49.2–96.5)	55.1 (36.4–81.9)	< 0.001
Zonulin (ng/mL)	38.2 ± 9.6	51.7 ± 12.3	66.4 ± 14.8	84.9 ± 17.1	< 0.001
I-FABP (pg/mL)	684 (512–890)	1012 (760–1340)	1580 (1190–2060)	2460 (1820–3210)	< 0.001
LPS (EU/mL)	0.49 ± 0.14	0.71 ± 0.21	0.98 ± 0.27	1.34 ± 0.36	< 0.001
Fecal calprotectin (µg/g)	86 (42–140)	268 (172–395)	612 (420–890)	1240 (860–1870)	< 0.001
CRP (mg/L)	3.1 (1.6–5.4)	7.8 (4.2–12.6)	18.5 (11.3–29.7)	42.6 (27.9–68.3)	< 0.001

Data are mean ± SD or median (interquartile range). Abbreviations as in Table 2.

3.4 Correlations with activity and barrier indices

Spearman analysis confirmed the pattern suggested by the stratified data. GDF-15 correlated strongly with the total Mayo score ($r = 0.72$), the Mayo endoscopic subscore ($r = 0.66$), fecal calprotectin ($r = 0.69$) and CRP ($r = 0.63$), and moderately with ESR ($r = 0.54$). eNAMPT showed a parallel but slightly weaker profile ($r = 0.68$, 0.61, 0.64 and 0.59 respectively). IL-22 correlated only moderately with these indices ($r = 0.46$ with the total Mayo score and $r = 0.44$ with calprotectin).

The divergence was most marked for barrier markers. GDF-15 correlated moderately to strongly with zonulin ($r = 0.61$), I-FABP ($r = 0.65$), LPS ($r = 0.57$) and urinary claudin-3 ($r = 0.49$), and eNAMPT similarly ($r = 0.58$, 0.55, 0.52 and 0.46). IL-22 correlated only weakly with the same markers, the association with urinary claudin-3 failing to reach significance altogether ($r = 0.18$, $P = 0.089$). Both GDF-15 and eNAMPT were inversely related to serum albumin ($r = −0.48$ and $−0.42$) and haemoglobin ($r = −0.41$ and $−0.37$). None of the three mediators was related to disease duration. The three analytes correlated with one another at an intermediate level, GDF-15 with eNAMPT most closely ($r = 0.58$) (Table 4).

Table 4: Spearman correlations between the index biomarkers and indices of disease activity and barrier integrity (n = 90).

Variable	GDF-15 (r / P)	eNAMPT (r / P)	IL-22 (r / P)
Total Mayo score	0.72 / < 0.001	0.68 / < 0.001	0.46 / < 0.001
Mayo endoscopic subscore	0.66 / < 0.001	0.61 / < 0.001	0.41 / < 0.001
Fecal calprotectin	0.69 / < 0.001	0.64 / < 0.001	0.44 / < 0.001
CRP	0.63 / < 0.001	0.59 / < 0.001	0.39 / < 0.001
ESR	0.54 / < 0.001	0.50 / < 0.001	0.33 / 0.002
Zonulin	0.61 / < 0.001	0.58 / < 0.001	0.29 / 0.006
I-FABP	0.65 / < 0.001	0.55 / < 0.001	0.24 / 0.024
LPS	0.57 / < 0.001	0.52 / < 0.001	0.21 / 0.047
Urinary claudin-3	0.49 / < 0.001	0.46 / < 0.001	0.18 / 0.089
Serum albumin	−0.48 / < 0.001	−0.42 / < 0.001	−0.22 / 0.037

Variable	GDF-15 (r / P)	eNAMPT (r / P)	IL-22 (r / P)
Haemoglobin	−0.41 / < 0.001	−0.37 / < 0.001	−0.19 / 0.073
Disease duration	0.17 / 0.11	0.12 / 0.26	0.08 / 0.45
Inter-marker correlation	with eNAMPT: 0.58 / < 0.001	with IL-22: 0.44 / < 0.001	with GDF-15: 0.39 / < 0.001

Abbreviations as in Tables 1 and 2.

3.5 Diagnostic Performance

For distinguishing patients from controls, eNAMPT gave the highest single-marker area under the curve at 0.93 (95% confidence interval 0.89–0.97), with a cut-off above 3.9 ng/mL yielding 88.9% sensitivity and 86.7% specificity. GDF-15 followed at 0.91 (0.86–0.96), zonulin at 0.89 (0.83–0.94) and IL-22 at 0.87 (0.81–0.93). Combining the three index markers raised the area under the curve to 0.97 (0.94–0.99), with 93.3% sensitivity and 91.1% specificity (Table 5a). For the clinically more demanding task of separating active disease (Mayo ≥ 3) from remission within the patient group, fecal calprotectin performed best among single markers, with an area under the curve of 0.90 at a threshold of 180 µg/g. GDF-15 was close behind at 0.88, followed by eNAMPT at 0.85 and IL-22 at 0.78. The three-marker panel again outperformed each component, reaching 0.93 (0.88–0.98) with 89.4% sensitivity and 87.5% specificity (Table 5b).

Table 5a: ROC analysis: discrimination of ulcerative colitis from healthy controls.

Marker	AUC (95% CI)	Cut-off	Sensitivity (%)	Specificity (%)	P value
GDF-15	0.91 (0.86–0.96)	> 720 pg/mL	85.6	88.9	< 0.001
eNAMPT	0.93 (0.89–0.97)	> 3.9 ng/mL	88.9	86.7	< 0.001
IL-22	0.87 (0.81–0.93)	> 23.5 pg/mL	80.0	84.4	< 0.001
Zonulin	0.89 (0.83–0.94)	> 40.2 ng/mL	82.2	86.7	< 0.001
Combined three-marker model	0.97 (0.94–0.99)	—	93.3	91.1	< 0.001

AUC, area under the curve; CI, confidence interval; ROC, receiver operating characteristic.

Table 5b: ROC analysis: discrimination of active disease (Mayo ≥ 3) from remission among patients.

Marker	AUC (95% CI)	Cut-off	Sensitivity (%)	Specificity (%)	P value
GDF-15	0.88 (0.81–0.95)	> 860 pg/mL	83.3	83.3	< 0.001
eNAMPT	0.85 (0.77–0.93)	> 5.1 ng/mL	78.8	79.2	< 0.001
IL-22	0.78 (0.68–0.88)	> 32.0 pg/mL	72.7	75.0	< 0.001
Fecal calprotectin	0.90 (0.84–0.96)	> 180 µg/g	86.4	87.5	< 0.001
Combined three-marker model	0.93 (0.88–0.98)	—	89.4	87.5	< 0.001

Abbreviations as in Table 5a.

3.6 Independent predictors of active disease

In univariable logistic regression, every biomarker examined was associated with active disease, as was extensive (E3) disease. After adjustment for age, sex, disease extent and therapy, three variables retained independent significance: GDF-15, with an adjusted odds ratio of 2.68 (1.49–4.82) per 500 pg/mL increment (P = 0.001); eNAMPT, 1.52 (1.11–2.08) per 1 ng/mL (P = 0.009); and zonulin, 1.38 (1.02–1.87) per 10 ng/mL (P = 0.038). IL-22 lost its univariable association in the adjusted model (adjusted odds ratio 1.14, 0.90–1.45; P = 0.28), as did I-FABP and disease extent. Neither age, sex nor biologic therapy was independently associated with activity (Table 6).

Table 6: Univariable and multivariable logistic regression for factors associated with active disease (Mayo ≥ 3).

Variable	Crude OR (95% CI)	P value	Adjusted aOR (95% CI)	P value
GDF-15 (per 500 pg/mL)	3.42 (2.05–5.71)	< 0.001	2.68 (1.49–4.82)	0.001
eNAMPT (per 1 ng/mL)	1.86 (1.42–2.44)	< 0.001	1.52 (1.11–2.08)	0.009
IL-22 (per 10 pg/mL)	1.41 (1.16–1.71)	0.001	1.14 (0.90–1.45)	0.28
Zonulin (per 10 ng/mL)	1.73 (1.31–2.28)	< 0.001	1.38 (1.02–1.87)	0.038
I-FABP (per 500 pg/mL)	1.95 (1.38–2.76)	< 0.001	1.29 (0.86–1.94)	0.22

Variable	Crude OR (95% CI)	P value	Adjusted aOR (95% CI)	P value
Disease extent E3 vs E1/E2	2.84 (1.12–7.20)	0.028	1.92 (0.68–5.41)	0.22
Age (per year)	1.01 (0.98–1.05)	0.47	1.02 (0.97–1.06)	0.51
Sex (male vs female)	1.23 (0.52–2.91)	0.64	1.08 (0.41–2.86)	0.88
Biologic therapy (yes vs no)	0.46 (0.12–1.74)	0.25	0.39 (0.09–1.68)	0.21

aOR, adjusted odds ratio; CI, confidence interval; OR, odds ratio. The multivariable model was adjusted for age, sex, disease extent and current therapy.

4. Discussion

This study provides the first simultaneous assessment of GDF-15, eNAMPT and IL-22 in ulcerative colitis together with a panel of circulating and urinary barrier markers, and the first such assessment in an Iraqi cohort. Three findings stand out. GDF-15 and eNAMPT rose in strict proportion to disease activity and remained independently associated with active disease after adjustment. IL-22 was elevated overall but followed an inverted-U trajectory, peaking in moderate disease and falling in severe disease, and did not survive multivariable adjustment. Finally, the combination of the three analytes discriminated both disease status and disease activity better than any single marker, including fecal calprotectin for the first task.

4.1 GDF-15 as a stress-derived, barrier-linked marker

The 2.5-fold elevation of GDF-15 in our patients and its stepwise increase across activity strata are consistent with the international literature. A Croatian cross-sectional study of 90 patients with IBD and 67 controls reported significantly higher serum GDF-15 in patients, with concentrations predicting severity independently of age, sex and CRP and correlating inversely with haemoglobin and iron [10]. A Czech series of 100 patients receiving biologic therapy found persistently raised GDF-15 irrespective of the agent used, with correlations to fibrinogen and IL-6 [11]. A Greek cohort of 193 patients reported elevations in both Crohn's disease and UC, although in UC the authors judged IL-6 the stronger activity index and considered the role of GDF-15 to require further evaluation [12]. Our correlation coefficients with the total Mayo score ($r = 0.72$), the endoscopic subscore ($r = 0.66$) and calprotectin ($r = 0.69$) are at the upper end of this range, which may reflect the relatively high proportion of endoscopically active patients and the exclusion of comorbidities known to raise GDF-15 independently.

The inverse correlations we observed with haemoglobin ($r = −0.41$) and albumin ($r = −0.48$) echo two separate strands of the literature. GDF-15 is an erythroid regulator that links ineffective erythropoiesis to hepcidin suppression, and in UC the anaemia signal has been reported to dominate the inflammatory signal in determining hepcidin concentration [14]. Whether GDF-15 in our cohort is principally a marker of mucosal inflammation, of the anaemia of chronic disease, or of both in combination cannot be resolved by a cross-sectional design and deserves a dedicated iron-status analysis.

The most mechanistically interesting observation is the moderate-to-strong association of GDF-15 with zonulin ($r = 0.61$), I-FABP ($r = 0.65$), LPS ($r = 0.57$) and urinary claudin-3 ($r = 0.49$). Until recently, such associations would have been interpreted as parallel consequences of inflammation. Experimental work published in 2025, however, demonstrated that GDF-15 acts directly on colonic organoids and T84 monolayers to reduce zonula occludens-1 and claudin-1 and to increase permeability, and reported correlations in patients between circulating GDF-15 and LBP [13]. Our data are compatible with that causal reading: GDF-15, induced by the mitochondrial unfolded protein response in stressed colonocytes, may feed back onto the epithelium to loosen tight junctions and amplify antigen exposure. If so, GDF-15 is not merely a severity gauge but a candidate therapeutic target in refractory UC.

4.2 eNAMPT as a circulating alarmin

eNAMPT showed the single best discrimination between patients and controls in our cohort (area under the curve 0.93 at a cut-off of 3.9 ng/mL), closely reproducing the Egyptian study of 85 newly diagnosed patients, which reported areas under the curve of 0.91 in UC and 0.97 in Crohn's disease at a visfatin threshold of 1.4 ng/mL, with positive correlations to CRP, ESR and fecal calprotectin, and higher concentrations in extensive (E3) disease [16]. A larger Polish investigation combining serum, leukocyte and bowel-tissue measurements found NAMPT up-regulated in both inflamed and quiescent colon, with serum concentrations tracking clinical and endoscopic activity in UC and a low

threshold indicating mucosal healing [15]. Earlier adipokine panels likewise identified visfatin as one of the few mediators consistently elevated in IBD [17], and visfatin has been linked to osteoporosis risk in IBD [18] and to proangiogenic signalling modifiable by vitamin D status [19].

The absolute concentrations reported across these studies differ considerably, which almost certainly reflects assay heterogeneity rather than biology: immunoassays for NAMPT vary in epitope specificity and in their ability to distinguish monomeric from dimeric enzyme. This is the principal obstacle to transferring any numerical cut-off between laboratories and is the reason our thresholds should be regarded as internally valid only until replicated on a standardised platform.

Mechanistically, eNAMPT is best understood as a damage-associated molecular pattern acting through TLR4. Work in diabetic coronary microvascular disease and in intra-amniotic inflammation has shown that neutralising eNAMPT with a monoclonal antibody reduces downstream cytokine production and improves outcomes in preclinical models [20,21]. Given the central role of TLR4 signalling and of bacterial product translocation in UC, and given the correlation we observed between eNAMPT and both LPS ($r = 0.52$) and LBP-associated barrier failure, an eNAMPT-directed strategy is a biologically coherent proposition for colitis and has not yet been formally tested.

4.3 The non-linear behaviour of IL-22

IL-22 showed the largest relative elevation over controls (3.4-fold) but the weakest relationship with severity, and its concentration fell by roughly a quarter between moderate and severe disease. This biphasic pattern is precisely what the mechanistic literature predicts. IL-22 is a reparative cytokine acting through STAT3 on the epithelium to induce antimicrobial peptides, mucins and proliferative programmes, and is required for Paneth-cell differentiation in human organoids [22,23]. Its induction through the aryl hydrocarbon receptor in group 3 innate lymphoid cells restores tight-junction protein expression and reduces permeability in experimental colitis [25]. On that reading, the rise from remission through moderate disease represents a mounting reparative response proportional to epithelial injury.

The fall in severe disease is more plausibly explained by exhaustion or attrition of the IL-22-producing compartment: in extensive, deeply ulcerated colitis, innate lymphoid cells and Th22 cells are depleted from a mucosa that has lost much of its epithelial surface, so the reparative signal collapses at precisely the point where it is most needed. An alternative, not mutually exclusive, explanation is that the same cytokine contributes to pathology at high local concentrations, since IL-22 drives CXC-chemokine expression and $CXCR2^{+}$ neutrophil recruitment into the colon, and enrichment of IL-22-regulated transcripts in UC biopsies predicts non-response to ustekinumab [24]. The loss of significance for IL-22 in our multivariable model (adjusted odds ratio 1.14, $P = 0.28$) is consistent with either reading: a marker whose concentration is not monotonic in severity cannot behave as a linear predictor of a binary activity outcome.

The practical implication is that IL-22 should not be used alone as an activity marker. Its value lies in the information it adds about the balance between injury and repair, which is why it contributed to the combined panel despite its weak univariable performance.

4.4 Barrier failure as the common axis

Every barrier marker we measured was elevated and every one rose with severity, confirming that in UC the epithelium is not merely inflamed but functionally permeable. The pattern we observed, with zonulin, I-FABP and LBP all raised, parallels findings in a Romanian IBD cohort that examined the same panel in relation to depression and reported correlations between barrier markers and systemic manifestations [26]. In primary sclerosing cholangitis, elevated LBP and soluble CD14 predicted transplantation-free survival, implicating gut leakage in extraintestinal outcomes [27], while in diarrhoea-predominant irritable bowel syndrome the combination of I-FABP and permeability testing identified a distinct high-permeability subgroup [28]. Zonulin's behaviour across diseases is not uniform, and its measurement is assay-dependent, which argues for interpreting it as part of a panel rather than in isolation — as we have done here.

The independent association of zonulin with active disease in our multivariable model (adjusted odds ratio 1.38 per 10 ng/mL) alongside GDF-15 and eNAMPT suggests that barrier dysfunction carries information about activity that is not fully captured by inflammatory markers. This supports a model in which stress-derived mediators and barrier failure form a self-reinforcing loop rather than a simple cause-and-effect sequence.

4.5 Findings in the Iraqi Context

The demographic profile of our cohort — a mean age of 38.6 years, a near-equal sex distribution and a predominance of left-sided and extensive disease — is consistent with previous Iraqi descriptions of UC [3,29,30]. Iraqi work on UC biomarkers has so far concentrated on the IL-17/IL-23 axis and on calprotectin. Serum IL-17A and IL-23 were reported to be significantly elevated in 30 Iraqi UC patients compared with controls [4], a finding replicated in a second local series of 100 IBD patients in which serum IL-23 separated patients from controls with high significance [5] and in a parallel study of circulating calprotectin, IL-17 and IL-23 [31]. Salivary IL-6 and calprotectin have also been shown to be raised in Iraqi UC patients and proposed as non-invasive diagnostic adjuncts [6]. Our data extend this body of work along a different axis, showing that cellular stress signalling and epithelial barrier failure are at least as informative as the classical Th17 cytokines, and that they can be captured from a single fasting serum sample.

This has particular relevance for Iraqi practice. Access to colonoscopy for serial activity assessment is constrained by capacity, cost and patient acceptability, and fecal calprotectin, although available, suffers from sampling reluctance and pre-analytical variability. A serum panel that reaches an area under the curve of 0.93 for active disease offers a realistic complement, provided that it is validated prospectively against endoscopy in a local population and that assay performance is standardised between centres.

4.6 Clinical Implications

Three implications follow from our findings. First, a patient with a GDF-15 above 860 pg/mL and an eNAMPT above 5.1 ng/mL has a high probability of endoscopically active disease and warrants objective reassessment regardless of symptom score, since symptoms and mucosal inflammation are discordant in a substantial minority of patients. Second, the combination of a high GDF-15 and a relatively low IL-22 may identify a subgroup in which epithelial injury outstrips reparative capacity; whether this subgroup responds differently to therapy is testable and clinically important. Third, both GDF-15 and eNAMPT are pharmacologically tractable, the former through GFRAL-directed agents developed for metabolic indications and the latter through neutralising monoclonal antibodies already in preclinical use, so the markers may eventually double as targets.

5. Limitations

Several limitations must temper interpretation. The design is cross-sectional and single-centre, so temporal sequence cannot be established and the associations we report are not evidence of causation; whether GDF-15 rises before, with or after barrier failure requires longitudinal sampling. The sample size, while adequate for the primary comparisons, left only fifteen patients in the severe stratum, which limits precision for the IL-22 decline and makes that observation hypothesis-generating rather than definitive. Patients were heterogeneous with respect to therapy, and although treatment was entered into the multivariable model, residual confounding by drug effects on each analyte cannot be excluded. We measured circulating and urinary markers only; without paired mucosal biopsies we cannot say whether serum concentrations reflect local colonic production or systemic spill-over. The cut-offs derived here were obtained in the same dataset in which they were tested and were not validated in an independent sample, so they are likely to be optimistic. Finally, immunoassays for NAMPT and zonulin are known to vary between manufacturers, which restricts the transferability of absolute values; multicentre work on a harmonised platform is needed before any threshold enters clinical use.

6. Conclusion

In this Iraqi case–control study, serum GDF-15, eNAMPT and IL-22 were all substantially elevated in ulcerative colitis, as were every circulating and urinary marker of intestinal barrier integrity examined. GDF-15 and eNAMPT increased in proportion to clinical and endoscopic activity, correlated with barrier failure and remained independently associated with active disease after multivariable adjustment, positioning them as stress-derived markers that are mechanistically coupled to epithelial permeability. IL-22 behaved as a reparative cytokine with a non-linear relationship to severity, peaking in moderate disease and declining when the mucosa was most extensively damaged. A panel combining the three analytes achieved excellent discrimination both of disease status and of disease activity, exceeding the performance of any single marker. Prospective, multicentre validation against endoscopic endpoints,

together with assay standardisation and paired mucosal sampling, is the necessary next step before these markers can be used to guide management.

Declarations

Ethical Approval: The study protocol was approved by the ethics committee of Al-Kadhimiya Teaching Hospital, Baghdad, Iraq, on 1 September 2024. No approval reference number was assigned. Written informed consent was obtained from all participants before enrolment.
Consent for Publication: Not applicable; no individually identifiable data are reported.
Availability of Data: The anonymised dataset is available from the corresponding author on reasonable request.
Conflicts of Interest: The authors declare no competing interests.
Funding. This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.
Author Contribution: GN conceived and designed the study, supervised participant recruitment and clinical data collection, carried out the laboratory analyses, performed the statistical analysis, and drafted and approved the final manuscript.
Acknowledgements: The authors thank the staff of the Gastroenterology Unit and the clinical laboratories of Al-Kadhimiya Teaching Hospital for their assistance, and the patients and volunteers who consented to participate.

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