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Serum IL-23, IL-6 and Lipopolysaccharide-Binding Protein Reflect Nutritional and Inflammatory Burden in Crohn's Disease: A Stratified Analysis by Malnutrition Universal Screening Tool and Harvey–Bradshaw Index in an Iraqi Cohort

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Abstract

Background: In Crohn's disease (CD), reliable serum biomarkers that simultaneously reflect both systemic inflammation and nutritional compromise are needed to guide clinical stratification, particularly in regional settings where endoscopy and faecal calprotectin are not routinely available. This study evaluated whether serum interleukin-23 (IL-23), interleukin-6 (IL-6) and lipopolysaccharide-binding protein (LBP) stratify Iraqi CD patients across the Malnutrition Universal Screening Tool (MUST) and the Harvey–Bradshaw Index (HBI), and explored their behavior in patients who achieved mucosal healing under infliximab.

Methodology: A hospital-based cross-sectional study was conducted at Al-Najaf Gastrointestinal Tract Hospital, Iraq, between November 2025 and February 2026. The cohort included 67 consecutive adults with established CD: 32 with active disease and 35 on long-term infliximab maintenance. Serum IL-23, IL-6 and LBP were measured by commercial ELISA (BT Lab, Shanghai); CRP and albumin were quantified on an SMT-120 automated analyzer (Seamaty). Participants were stratified by MUST risk (low/medium/high) and HBI category (remission/mild/moderate). Non-parametric Kruskal–Wallis and Mann–Whitney U tests were used; Spearman correlations linked biomarkers to continuous clinical indices.

Results: Serum LBP, IL-23 and IL-6 concentrations rose monotonically across MUST categories (all $P \leq 0.004$) and HBI activity categories (all $P \leq 0.013$), with the steepest gradient for LBP (low-risk 7.72 vs high-risk 11.43 ng/mL; $P < 0.001$). LBP correlated positively with MUST score ($\rho = 0.50$), HBI ($\rho = 0.37$) and CRP ($\rho = 0.47$), and negatively with BMI ($\rho = -0.47$; all $P < 0.001$). CRP and albumin showed no significant within-CD correlations. In infliximab-treated patients with mucosal healing, LBP, IL-23, IL-6 and CRP were directionally lower than in non-healers, but differences did not reach statistical significance ($P \geq 0.073$) in this underpowered subgroup.

Conclusion: Serum IL-23, IL-6 and LBP are quantitative indicators of both nutritional and inflammatory burden in Crohn's disease, outperforming CRP and albumin for stratifying clinical severity within CD patients. These accessible serum biomarkers merit prospective evaluation as stratification tools in Middle-Eastern IBD cohorts.

البروتينات المصلية IL-23 و IL-6 والبروتين الرابط لعديد السكاريد الدهني تعكس العبء الغذائي والالتهابي في داء كرون: تحليل طبقي وفق أداة الفحص الشاملة لسوء التغذية ومؤشر هارفي–برادشو في كوهورت عراقي

أحمد عفيف عثمان ووسن سامي حميد

الخلاصة

المقدمة: في داء كرون (CD)، تُعدّ المؤشرات الحيوية المصلية الموثوقة التي تعكس في آنٍ واحد كلاً من الالتهاب الجهازي والقصور الغذائي ضرورية لتوجيه التصنيف السريري، وبخاصة في الإعدادات الإقليمية التي لا يتوفر فيها التنظير الداخلي وفحص الكالبروتكتين البرازي بشكل اعتيادي. هدفت هذه الدراسة إلى تقييم ما إذا كانت تراكيز IL-23 و IL-6 و LBP في المصل تستطيع تصنيف مرضى داء كرون العراقيين وفق أداة الفحص الشاملة لسوء التغذية (MUST) ومؤشر هارفي–برادشو (HBI)، واستكشاف سلوكها لدى المرضى الذين حقّقوا التئامًا مخاطيًا تحت علاج الإنفليكسيماب.

المرضى وطرق العمل: في تحليل مقطعي (تشرين الثاني 2025 – شباط 2026؛ مستشفى الجهاز الهضمي في النجف، العراق) دُرس 67 بالغًا متتاليًا من مرضى داء كرون المُشخَّصين. قِيست المؤشرات IL-23 و IL-6 و LBP في المصل بطريقة الإليزا التجارية (BT Lab، شنغهاي)؛ بينما قُدّر البروتين المتفاعل C (CRP) والألبومين على محلل SMT-120 الآلي (Seamaty). صُنّف المشاركون وفق درجة الخطر بـ MUST (منخفض/متوسط/مرتفع) وفئة HBI (هدأة/خفيف/متوسط). كما أُجري تحليل فرعي مُحدّد مسبقًا للمقارنة بين مرضى الإنفليكسيماب الذين حقّقوا التئامًا مخاطيًا (ن = 12) ومن لم يحقّقوه (ن = 23). استُخدمت اختبارات كروسكال–والس ومان–ويتني اللامعلميّة؛ وارتباطات سبيرمان لربط المؤشرات بالمؤشرات السريرية المستمرة.

النتائج: ارتفعت تراكيز LBP و IL-23 و IL-6 المصلية بصورة رتيبة عبر فئات MUST (جميع $P \le 0.004$) وعبر فئات نشاط HBI (جميع $P \le 0.013$)، وكان أحدّ تدرج لـ LBP (الخطر المنخفض 7.72 مقابل المرتفع 11.43 نانوغرام/مل؛ $P < 0.001$). ارتبط LBP إيجابيًا بدرجة (MUST ($\rho = 0.50$، و (HBI ($\rho = 0.37$)، و (CRP ($\rho = 0.47$)، وسلبيًا بمؤشر كتلة الجسم ($\rho = -0.47$؛ جميعها $P < 0.001$). لم يُظهر CRP والألبومين ارتباطات معنوية مع HBI أو BMI أو MUST. وفي مرضى الإنفليكسيماب الذين حقّقوا التئامًا مخاطيًا، كانت قيم LBP و IL-23 و IL-6 و CRP أقل اتجاهيًا مقارنة بغير الملتئمين، إلّا أن الفروق لم تبلغ المعنوية الإحصائية ($P \ge 0.073$) في هذه المجموعة الفرعية ذات القدرة الإحصائية المحدودة.

الاستنتاج: تُعدّ مؤشرات IL-23 و IL-6 و LBP المصلية مؤشرات كمّية على كلٍ من العبء الغذائي والالتهابي في داء كرون، وتتفوق على CRP والألبومين في تصنيف الشدة السريرية ضمن مرضى داء كرون. تستحق هذه المؤشرات المصلية المتاحة تقييمًا مستقبليًا كأدوات تصنيف في كوهورتات أمراض الأمعاء الالتهابية في الشرق الأوسط، وبخاصة حيث يكون فحص الكالبروتكتين البرازي والمتابعة التنظيرية الروتينية مقيّدًا.

1. Introduction

Crohn's disease (CD) is a chronic, transmural, immune-mediated inflammatory bowel disease (IBD) in which systemic inflammation and protein-energy malnutrition are tightly coupled and mutually reinforcing (Torres et al., 2017). Malnutrition affects 20–85% of CD patients depending on disease phase and population setting, is independently associated with complications, hospitalisation and surgery, and has a negative impact on quality of life and response to therapy (Massironi et al., 2013; Bischoff et al., 2023). In low- and middle-income settings such as Iraq, where nutritional reserves are often already compromised and endoscopic monitoring is not universally available, simple and accessible clinical and serum tools for identifying high-risk patients are particularly valuable (Mosli et al., 2021; Mohammed and Amin, 2022).

The Malnutrition Universal Screening Tool (MUST), developed by the British Association for Parenteral and Enteral Nutrition (BAPEN), is a validated five-step screening instrument widely used in gastroenterology services to stratify adult patients into low, medium and high nutritional-risk categories (Elia, 2003; Stratton et al., 2004). The European Society for Clinical Nutrition and Metabolism (ESPEN) specifically endorses MUST for nutritional screening in IBD (Forbes et al., 2017). In parallel, the Harvey–Bradshaw Index (HBI) is the most widely used clinical activity score in CD; it stratifies patients into remission (HBI ≤ 4), mild (5–7), moderate (8–16) and severe (≥ 17) activity and shows excellent agreement with the more complex Crohn's Disease Activity Index (Harvey and Bradshaw, 1980; Best, 2006). Although MUST and HBI capture complementary dimensions of patient state, their biological correlates in the serum proteome remain incompletely characterised, especially in Middle-Eastern populations. Three biologically distinct serum proteins deserve specific attention in this context. Interleukin-23 (IL-23) is a heterodimeric cytokine that stabilises pathogenic Th17 cells, sustains mucosal production of IL-17A/IL-22/GM-CSF, and is an established therapeutic target in CD via risankizumab, ustekinumab and mirikizumab (Sewell and Kaser, 2022; Schmitt et al., 2021; Fanizza et al., 2023). Interleukin-6 (IL-6) drives hepatic acute-phase protein synthesis (including C-reactive protein and LBP) through gp130–STAT3 signalling and has been shown to track clinical activity and biological treatment response in IBD cohorts (Mavropoulou et al., 2020; Caviglia et al., 2020). Lipopolysaccharide-binding protein (LBP) is a hepatocyte-derived class-I acute-phase protein whose serum concentration reflects ongoing bacterial translocation across a disrupted intestinal barrier; it has been proposed as a surrogate for translocation-driven inflammation in CD (Schumann, 2011; Pastor Rojo et al., 2007; Linares et al., 2021). Despite the biological coherence of the IL-23/IL-6/LBP axis, little is known about how these biomarkers distribute across clinical strata within CD patients — that is, whether they discriminate not only CD from health (a question addressed elsewhere in the diagnostic literature) but also between sub-groups of CD patients stratified by nutritional risk and by clinical activity. Most available data come from European cohorts (Lakatos et al., 2011; Toris et al., 2024), and Iraqi data are scarce (Hassan and Delmany, 2018; Abdulla et al., 2025; Qusay et al., 2024). CRP, the biomarker most widely used in clinical practice, has well-known limitations: it is elevated in only 50–60% of patients with endoscopically active CD and correlates only moderately with the HBI, making complementary biomarkers highly desirable (Peyrin-Biroulet et al., 2014; Clough et al., 2024). We therefore conducted a cross-sectional analysis of 67 Iraqi adults with established CD to address three questions: (i) do serum IL-23, IL-6 and LBP show dose–response relationships with MUST-defined nutritional risk; (ii) do they show dose–response relationships with HBI-defined clinical activity; and (iii) in the subgroup on long-term infliximab maintenance, how do these biomarkers behave according to mucosal-healing status? We hypothesised that all three biomarkers, together with the LBP/albumin ratio, would rise monotonically across both MUST and HBI strata, that LBP and the LBP/albumin ratio would show the strongest gradient (because they integrate inflammatory and nutritional signals), and that CRP and albumin alone would be less sensitive stratifiers of within-CD burden.

2. Materials and Methods

2.1. Study Design, Setting and Ethics

We performed a single-centre cross-sectional analysis of adult Crohn's disease patients recruited between November 2025 and February 2026 at the Al-Najaf Gastrointestinal Tract Center (GIT Hospital), Najaf Al-Ashraf, Iraq. Ethical approval was obtained from the Ethics Committee of the Ministry of Health, Najaf Health Directorate, Training and Human Development Center (Reference No. 4148, dated November 2025). All procedures conformed to the Declaration of Helsinki. Written informed consent was obtained from every participant. Reporting follows the STROBE statement for observational studies (von Elm et al., 2007).

2.2. Participants

Consecutive adults with an established diagnosis of CD made per the ECCO–ESGAR Guideline for Diagnostic Assessment in IBD (Maaser et al., 2019) were eligible. The present study included only the CD patients of the parent cohort (n = 67): 32 with active CD (HBI ≥ 5 plus at least one objective inflammatory marker) and 35 on long-term (≥ 12 months) infliximab maintenance at 5 mg/kg every 8 weeks with dose/interval optimisation as clinically indicated. Exclusion criteria were: coexistent ulcerative colitis or unclassified IBD; malignancy; pregnancy or lactation; systemic corticosteroids or non-infliximab immunomodulators within 4 weeks; chronic liver or kidney disease; other active autoimmune disease; and bowel surgery within 12 weeks or the presence of an ostomy. Elevated CRP and unintentional weight loss were not exclusion criteria, as both are expected features of the study population.

2.3. Clinical and Nutritional Instruments

Disease activity was scored using the Harvey–Bradshaw Index (HBI), with the validated categories of remission (≤ 4), mild activity (5–7), moderate activity (8–16) and severe activity (≥ 17) (Harvey and Bradshaw, 1980; Best, 2006). Nutritional risk was scored using the Malnutrition Universal Screening Tool (MUST), which integrates BMI, unintentional weight loss over 3–6 months and an acute-disease effect into low, medium and high risk categories (Elia, 2003; Stratton et al., 2004). Disease location and behaviour were recorded by the Montreal classification (L1/L2/L3; B1/B2/B3; A1/A2/A3; perianal modifier) (Satsangi et al., 2006). BMI was calculated from height and weight measured on a calibrated stadiometer and scale and classified by WHO cut-offs. Mucosal healing was defined endoscopically per standard criteria, applied to the infliximab-treated subgroup (n = 35) within the 12-week window nearest to sampling (Turner et al., 2021; Gordon et al., 2024).

2.4. Sample Collection and Biomarker Measurement

Fasting peripheral venous blood (5 mL) was drawn into a plain serum-separator tube, allowed to clot for 30 min, centrifuged at 3,000 × g for 10 min within 2 h, aliquoted, and stored at −80 °C; freeze–thaw cycles were limited to one. Serum IL-6, IL-23 and LBP were quantified by sandwich ELISA (BT Lab; Shanghai Korain Biotech Co. Ltd, Shanghai, China; catalogue numbers E0090Hu, E0074Hu and E0360Hu, respectively) per manufacturer instructions, with intra-assay CV < 8% and inter-assay CV < 10%. Samples were measured in duplicate with a four-parameter logistic standard curve on each plate; absorbance was read at 450 nm. CRP (Giesse Diagnostics CRP-Q; REF 7710/7732/7783/7782) and serum albumin (Giesse Diagnostics BCG; REF 0027/0027/2/0028) were measured on a SMT-120 fully automated random-access biochemistry analyser (Geno Tek, USA) in Fixed-Time mode. Daily two-level quality controls were run. The LBP/albumin ratio was calculated as LBP (ng/mL) ÷ albumin (g/dL) and is presented here as a complementary clinical index.

2.5. Statistical Analysis

Continuous variables are presented as mean ± SD when normally distributed and as median (interquartile range) when non-normally distributed; categorical variables as n (%). Between-category comparisons across three MUST or HBI strata were performed with the Kruskal–Wallis H-test for continuous variables and with Pearson's χ^2 (or Fisher's exact) for categorical variables; pairwise comparisons were performed with the Mann–Whitney U-test. For the mucosal-healing subgroup comparison (n = 12 vs n = 23) the Mann–Whitney U-test was used; because the subgroup is underpowered for conventional P-values, results are reported alongside median fold changes as effect sizes, per STROBE item 16b (von Elm et al., 2007). Correlations between biomarkers and continuous clinical indices were assessed by Spearman's ρ. Two-sided $P < 0.05$ was considered statistically significant. Analyses were performed with Python 3.11 (SciPy, scikit-learn, statsmodels), with cross-checks in IBM SPSS v27 and MedCalc v22.

3. Results

3.1. Baseline Characteristics Stratified by Nutritional Risk

Clinical and demographic characteristics of the 67 CD patients, stratified by MUST category, are shown in Table1. Thirty-eight patients (56.7%) were categorised as low nutritional risk, 11 (16.4%) as medium risk and 18 (26.9%) as high risk. Age and sex did not differ significantly between MUST categories (both $P \geq 0.628$), but BMI decreased sharply with increasing MUST risk (25.21 ± 4.51 vs 23.66 ± 5.62 vs 19.52 ± 2.88 kg/m²; $P < 0.001$), as expected given that BMI is a MUST component. Unintentional weight loss and reduced/absent appetite were substantially more frequent at higher MUST risk (both $P < 0.001$). Clinically, HBI score rose from a median of 4 (IQR 3–6) in low-risk patients to 6 (4–8) in medium-risk to 8 (6–10) in high-risk patients ($P < 0.001$), and the proportion of patients in moderate HBI activity increased from 13.2% to 36.4% to 66.7% across the three categories. The proportion currently on infliximab maintenance decreased with rising MUST risk (68.4% vs 45.5% vs 22.2%; $P = 0.002$), suggesting that nutritional compromise and persistent clinical activity co-segregate. Montreal disease location did not differ significantly across MUST strata ($P = 0.412$).

Table1: Clinical Characteristics of Crohn's Disease Patients (N = 67), Stratified by Malnutrition Universal Screening Tool (MUST) Nutritional-Risk Category

Variable	Low Risk (n = 38)	Medium Risk (n = 11)	High Risk (n = 18)	P value
Demographic characteristics				
Age (years), mean ± SD	29.8 ± 10.6	27.1 ± 9.5	30.2 ± 11.2	0.628
Male sex, n (%)	26 (68.4)	7 (63.6)	11 (61.1)	0.814
BMI (kg/m²), mean ± SD	25.21 ± 4.51	23.66 ± 5.62	19.52 ± 2.88	**<0.001**
BMI category, n (%)				
Underweight	0 (0.0)	2 (18.2)	6 (33.3)	
Normal weight	19 (50.0)	6 (54.6)	11 (61.1)	
Overweight	10 (26.3)	1 (9.1)	1 (5.6)	
Obese	9 (23.7)	2 (18.2)	0 (0.0)	
Nutritional and inflammatory markers				
Weight loss, n (%)	6 (15.8)	6 (54.6)	11 (61.1)	**<0.001**
Reduced or absent appetite, n (%)	8 (21.1)	7 (63.6)	13 (72.2)	**<0.001**
Elevated CRP, n (%)	10 (26.3)	6 (54.6)	11 (61.1)	0.018
Serum albumin (g/dL), median (IQR)	4.65 (4.40–4.85)	4.50 (4.30–4.80)	4.45 (4.10–4.78)	0.094
Disease characteristics				
Disease duration (months), mean ± SD	24.7 ± 18.4	18.8 ± 15.3	14.4 ± 17.0	0.068
HBI score, median (IQR)	4 (3–6)	6 (4–8)	8 (6–10)	**<0.001**
HBI category, n (%)				**<0.001**
Remission (≤4)	22 (57.9)	4 (36.4)	3 (16.7)	
Mild activity (5–7)	11 (28.9)	3 (27.3)	3 (16.7)	
Moderate activity (8–16)	5 (13.2)	4 (36.4)	12 (66.7)	

Montreal disease location, n (%)				
L1 (ileal)	18 (47.4)	6 (54.6)	7 (38.9)	
L2 (colonic)	2 (5.3)	0 (0.0)	1 (5.6)	
L3 (ileocolonic)	12 (31.6)	4 (36.4)	5 (27.8)	
Mucosal healing, n (%)	6 (15.8)	1 (9.1)	5 (27.8)	**0.372***
Current infliximab therapy, n (%)	26 (68.4)	5 (45.5)	4 (22.2)	**0.002**

Data are presented as mean ± standard deviation (SD), median (interquartile range [IQR]), or number (%), as appropriate. Continuous variables were compared using one-way analysis of variance (ANOVA) or the Kruskal–Wallis test according to data distribution. Categorical variables were compared using Pearson's χ^2 test or Fisher's exact test, as appropriate. BMI: body mass index; CRP: C-reactive protein; HBI: Harvey–Bradshaw Index; L1: ileal disease; L2: colonic disease; L3: ileocolonic disease.

3.2. Serum Biomarkers Stratified by MUST Nutritional Risk

Serum biomarker concentrations stratified by MUST risk are presented in Table2 and visualized in Fig.1. All three novel biomarkers rose monotonically with nutritional risk category. LBP median increased from 7.72 ng/mL in low-risk patients to 9.43 in medium-risk and 11.43 in high-risk patients (H = 15.741; P < 0.001). IL-23 and IL-6 followed the same pattern (IL-23: 81.68 → 109.78 → 98.70 pg/mL, P = 0.004; IL-6: 65.12 → 71.45 → 77.09 pg/mL, P = 0.002). The LBP/albumin ratio showed a particularly clean gradient (1.65 → 2.00 → 2.63; H = 14.922, P < 0.001). CRP increased across categories (3.10 → 5.80 → 7.58 mg/L) but with a substantially weaker effect (P = 0.031). These patterns indicate that the IL-23/IL-6/LBP axis captures nutritional as well as inflammatory burden.

Table2: Serum Biomarker Concentrations in Crohn's Disease Patients Stratified by MUST Nutritional-Risk Category (N = 67).

Biomarker	Low risk (n = 38)	Medium risk (n = 11)	High risk (n = 18)	H	P
LBP (ng/mL)	7.72 (5.79–9.35)	9.43 (7.21–13.64)	11.43 (9.60–13.10)	15.741	<0.001
IL-23 (pg/mL)	81.68 (69.05–92.83)	109.78 (60.15–121.75)	98.70 (92.61–119.25)	10.970	0.004
IL-6 (pg/mL)	65.12 (58.73–68.46)	71.45 (64.17–78.16)	77.09 (66.82–79.20)	12.734	0.002
CRP (mg/L)	3.10 (1.47–8.65)	5.80 (2.10–18.35)	7.58 (3.85–19.40)	6.942	0.031
LBP / Albumin ratio	1.65 (1.29–2.03)	2.00 (1.52–2.92)	2.63 (2.14–2.99)	14.922	<0.001

Values are median (interquartile range). H = Kruskal–Wallis H statistic. Abbreviations: LBP, lipopolysaccharide-binding protein; IL, interleukin; CRP, C-reactive protein; MUST, Malnutrition Universal Screening Tool.

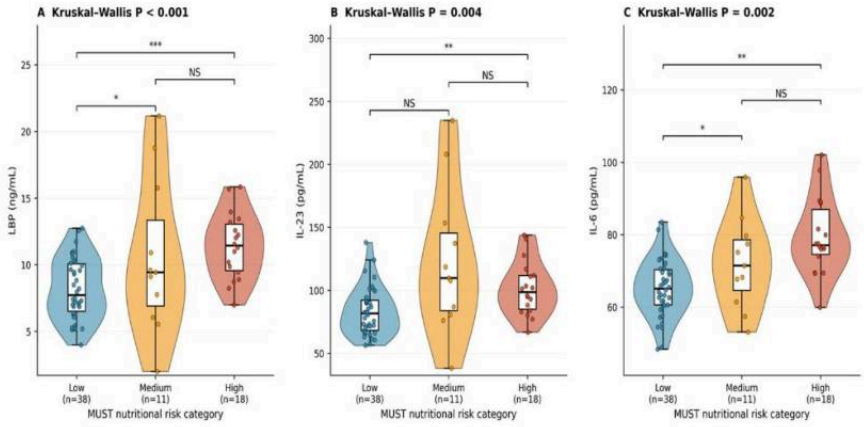

Figure1: Serum Concentrations Of LBP, IL-23 And IL-6 In Crohn's Disease Patients Stratified by Malnutrition Universal Screening Tool (MUST) Nutritional-Risk Category. Violin plots show the full distribution of each biomarker with embedded box plots (box = interquartile range; central bar = median; whiskers = 1.5 × IQR) and individual jittered data points. Panels: (A) LBP (ng/mL); (B) IL-23 (pg/mL); (C) IL-6 (pg/mL). Significance brackets indicate Mann–Whitney U pairwise comparisons: *, P < 0.05; **, P < 0.01; ***, P < 0.001; NS, not significant. All three biomarkers rose monotonically with increasing nutritional risk.

3.3. Serum Biomarkers Stratified by HBI Disease Activity

A parallel pattern emerged when patients were stratified by HBI activity category Table3 and Fig.2. LBP medians increased from 6.90 ng/mL in remission to 9.43 in mild activity and 13.02 in moderate activity (H = 9.942; P = 0.007). IL-23 rose from 80.56 → 95.49 → 101.78 pg/mL (P = 0.013), and IL-6 from 64.62 → 68.45 → 76.76 pg/mL (P = 0.010). The LBP/albumin ratio again provided the cleanest monotonic gradient across HBI strata (1.48 → 1.95 → 2.74; P = 0.006). CRP discriminated moderate activity from remission (8.45 vs 2.70 mg/L; P = 0.016) but did not significantly distinguish remission from mild activity. Notably, the largest relative rise across the activity spectrum was observed for LBP (1.9-fold from remission to moderate activity), exceeding CRP (3.1-fold but with wider variance), IL-23 (1.26-fold) and IL-6 (1.19-fold).

Table3: Serum Biomarker Concentrations In Crohn's Disease Patients Stratified By Harvey–Bradshaw Index (HBI) Activity Category (N = 67).

Biomarker	Remission (n = 29)	Mild activity (n = 17)	Moderate activity (n = 21)	H	P
LBP (ng/mL)	6.90 (5.77–9.43)	9.43 (7.66–11.21)	13.02 (8.54–13.57)	9.942	0.007
IL-23 (pg/mL)	80.56 (62.09–89.81)	95.49 (82.03–101.23)	101.78 (89.16–121.20)	8.694	0.013
IL-6 (pg/mL)	64.62 (58.99–67.83)	68.45 (65.99–76.78)	76.76 (64.31–79.14)	9.204	0.010
CRP (mg/L)	2.70 (1.40–5.85)	4.35 (2.20–9.75)	8.45 (3.85–21.30)	8.215	0.016
LBP / Albumin ratio	1.48 (1.20–1.92)	1.95 (1.58–2.45)	2.74 (1.85–2.95)	10.184	0.006
Values are median (interquartile range). H = Kruskal–Wallis H statistic. HBI remission ≤ 4; mild activity 5–7; moderate activity 8–16					

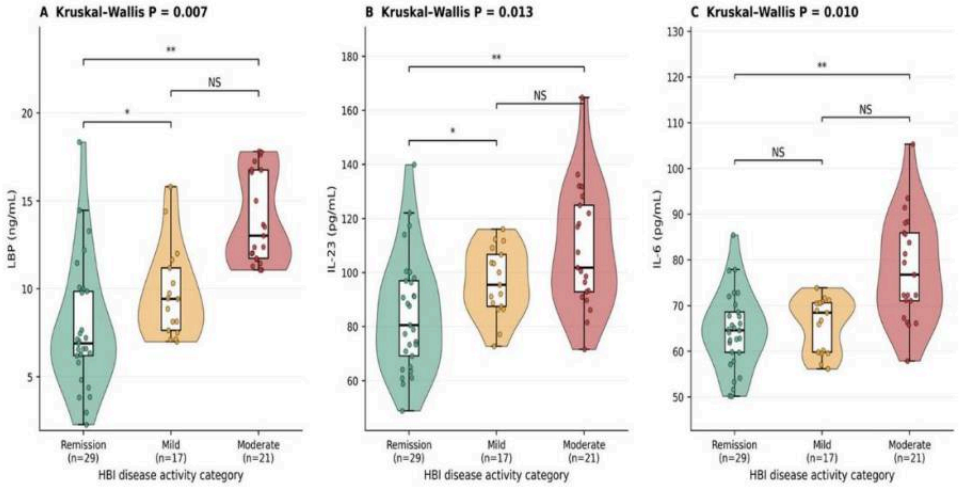

Figure2: Serum Concentrations of LBP, IL-23 And IL-6 In Crohn's Disease Patients Stratified by Harvey–Bradshaw Index (HBI) Disease-Activity Category. Violin plots with embedded box plots and individual data points. Panels: (A) LBP (ng/mL); (B) IL-23 (pg/mL); (C) IL-6 (pg/mL). Significance brackets: *, P < 0.05; **, P < 0.01; NS, not significant (Mann–Whitney U with Bonferroni adjustment). Biomarker concentrations rose monotonically with HBI activity; the largest relative rise across remission → mild → moderate activity was observed for LBP.

3.4. Continuous Biomarker–Clinical Correlations

Spearman correlation analyses within the CD cohort (n = 67) showed that LBP was positively correlated with MUST score (ρ = 0.499; P < 0.001), HBI (ρ = 0.367; P = 0.002) and CRP (ρ = 0.470; P < 0.001), and negatively correlated with BMI (ρ = −0.470; P < 0.001) and disease duration (ρ = −0.353; P = 0.003). IL-23 and IL-6 showed the same pattern at slightly lower magnitude (MUST ρ = 0.364 and 0.420, respectively; HBI ρ = 0.321 and 0.377, respectively). The LBP/albumin ratio showed the strongest clinical correlations of any biomarker evaluated (MUST ρ = 0.504; BMI ρ = −0.464; HBI ρ = 0.408; all P < 0.001). By contrast, CRP showed no significant correlation with HBI (P = 0.099), BMI (P = 0.480) or MUST (P = 0.150), and albumin showed no significant correlation with any clinical index (all P ≥ 0.104). Representative scatter plots with regression lines are shown in Fig.3.

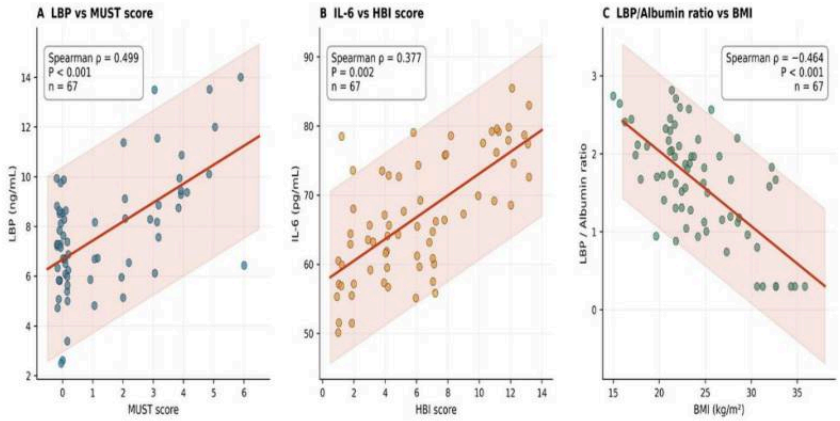

Figure 3: Continuous Relationships Between Serum Biomarkers and Clinical Parameters in Crohn's Disease Patients (N = 67). Scatter Plots with Linear Regression Lines And 95% Confidence Bands. (A) LBP versus MUST score (Spearman ρ = 0.499, P < 0.001). (B) IL-6 versus HBI score (ρ = 0.377, P = 0.002). (C) LBP/Albumin ratio versus BMI (ρ = −0.464, P < 0.001).

3.5. Biomarkers in the Infliximab-Maintained Subgroup by Mucosal-Healing Status

Within the infliximab-treated subgroup (n = 35), 12 patients (34.3%) had achieved mucosal healing (MH) at the endoscopy performed nearest to sampling, and 23 (65.7%) had not. Table4 (Panel A) summarizes infliximab treatment characteristics. Panel B and Fig.4. show that mucosally-healed patients had consistently lower median biomarker concentrations than non-healers (LBP 6.20 vs 8.11 ng/mL; IL-23 65.09 vs 82.03 pg/mL; IL-6 63.41 vs 66.63 pg/mL; CRP 2.05 vs 4.20 mg/L) and slightly higher albumin (4.65 vs 4.50 g/dL). However, given the modest subgroup size, these between-group differences did not reach conventional statistical significance (P ≥ 0.073 for all comparisons). The strongest signal was for IL-23 (P = 0.073, trend). These findings — with directionally consistent patterns but limited statistical power — are best interpreted as hypothesis-generating.

Table4: Infliximab Treatment Characteristics (Panel A) And Serum Biomarker Concentrations by Mucosal-Healing Status (Panel B) In Infliximab-Maintained Crohn's Disease Patients (N = 35).

Panel B. Serum biomarkers by mucosal-healing status in infliximab-treated patients				
Biomarker	**MH (n = 12)**	**Non-MH (n = 23)**	**U**	**P**
LBP (ng/mL)	6.20 (5.66–8.11)	8.11 (6.51–9.84)	99.0	0.181
IL-23 (pg/mL)	65.09 (61.13–80.01)	82.03 (74.33–94.86)	86.0	0.073
IL-6 (pg/mL)	63.41 (59.23–66.26)	66.63 (61.77–68.46)	98.0	0.170
CRP (mg/L)	2.05 (0.78–8.07)	4.20 (2.40–18.90)	95.0	0.139
Albumin (g/dL)	4.65 (4.50–4.93)	4.50 (4.20–4.80)	178.5	0.163

LBP / Albumin ratio	1.35 (1.15–1.75)	1.80 (1.43–2.21)	93.0	0.122
Panel A: Values are mean ± SD and median (min–max). Panel B: Values are median (interquartile range). U = Mann–Whitney U statistic. The comparison (n = 12 vs n = 23) is underpowered; no comparison reached conventional significance (all P ≥ 0.073).				

Panel A. Infliximab treatment characteristics (n = 35)		
Characteristic	**Mean ± SD**	**Median (min–max)**
Dose (mg)	344.9 ± 93.5	300.0 (200.0–560.0)
Duration of treatment (months)	23.9 ± 12.3	20.0 (12.0–55.0)
Infusion interval (weeks)	7.3 ± 1.0	8.0 (6.0–8.0)
Number of doses received	16.9 ± 6.6	16.0 (6.0–32.0)

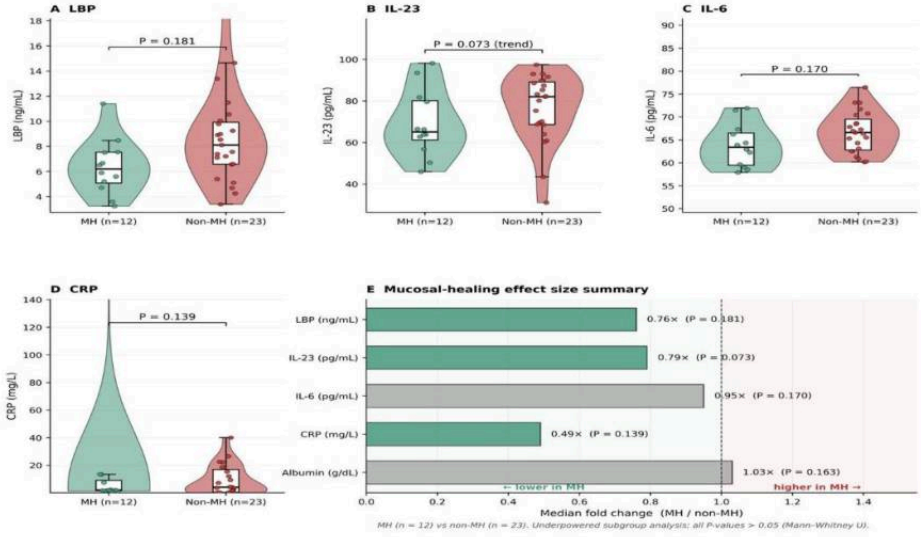

Figure4: Mucosal-Healing Subgroup Analysis in Infliximab-Maintained Crohn's Disease (N = 35). Panels (A)–(D): violin plots of serum LBP, IL-23, IL-6 and CRP in patients with mucosal healing (MH, n = 12; green) versus those without (non-MH, n = 23; red). P-values from Mann–Whitney U tests; IL-23 shows a trend (P = 0.073). (E) Bar plot of median fold changes (MH / non-MH). All four inflammatory biomarkers were directionally lower in MH;

4. Discussion

In this stratified analysis of 67 Iraqi Crohn's disease patients, serum LBP, IL-23 and IL-6 varied in a dose–response manner across both nutritional-risk categories (MUST) and clinical-activity categories (HBI). The LBP/albumin ratio consistently provided the cleanest monotonic gradient across both stratification schemes. Continuous correlations were concordant with the categorical analyses: LBP and the LBP/albumin ratio correlated strongly with MUST ($\rho = 0.50$ and 0.50, respectively), HBI ($\rho = 0.37$ and 0.41), BMI ($\rho = -0.47$ and -0.46) and CRP ($\rho = 0.47$), whereas CRP and albumin in isolation showed no significant within-CD correlation with clinical or nutritional indices. In the infliximab-treated subgroup, patients with mucosal healing showed directionally lower concentrations of all inflammatory biomarkers compared with non-healers, although differences did not reach significance in this modest subgroup. These observations extend previous work by demonstrating that the IL-23/IL-6/LBP axis is not only a diagnostic discriminator of CD but also a stratifier of disease burden within the CD population. Malnutrition in CD is neither incidental nor merely a consequence of reduced intake: it arises from a triad of decreased absorption, increased catabolism driven by pro-inflammatory cytokines, and chronic enteric protein loss (Massironi et al., 2013; Bischoff et al., 2023). The three inflammatory biomarkers examined here are

mechanistically linked to this triad. IL-6 directly drives muscle proteolysis and hepatic acute-phase protein synthesis through STAT3 signalling and contributes to anorexia of inflammation (Mavropoulou et al., 2020). IL-23 sustains Th17-mediated mucosal damage that impairs absorptive surface area and contributes to enteric protein loss (Sewell and Kaser, 2022; Schmitt et al., 2021). LBP reflects ongoing bacterial translocation, which in turn triggers systemic cytokine release and sustains the catabolic state (Pastor Rojo et al., 2007; Linares et al., 2021). Our findings suggest that the three biomarkers, operating at different tiers of the inflammatory cascade, converge on a common clinical phenotype of combined nutritional and inflammatory burden. The LBP/albumin ratio — placing a bacterial-translocation signal in the numerator over a negative acute-phase protein denominator — captures this combined burden most efficiently and is the strongest within-CD stratifier of the biomarkers examined. The MUST screening tool is recommended by ESPEN as the first-line nutritional screening instrument in IBD and has been validated across gastroenterology populations (Elia, 2003; Stratton et al., 2004; Forbes et al., 2017). In unselected hospital outpatients and inpatients, Stratton et al. (2004) demonstrated that MUST had excellent concurrent validity and predicted clinical outcomes. In IBD specifically, MUST performance has been corroborated by several cohorts. Sandhu et al. (2016) in a UK IBD clinic reported an 18% prevalence of medium-or-high MUST risk in outpatient IBD, increasing to > 40% in patients with active disease. Cass and Charlton (2022), in a recent European IBD nutrition review, argued that MUST outperforms BMI and unintentional weight loss alone because it integrates acute disease effect. Our study adds two observations to this literature: first, serum biomarkers parallel MUST categorisation in a dose–response manner, which suggests that MUST captures a biological inflammation–nutrition gradient rather than purely anthropometric variation; and second, in a Middle-Eastern CD population, the proportion of high-risk MUST patients (26.9%) is comparable to European reports, which has implications for the external generalisability of ESPEN-aligned nutrition pathways in Iraqi practice. HBI is widely used in CD trials and clinical practice because it is simple, reproducible and highly correlated with the full Crohn's Disease Activity Index ($r > 0.90$) without the need for a weekly diary (Harvey and Bradshaw, 1980; Best, 2006). Despite that utility, HBI is a symptomatic index and does not directly reflect mucosal inflammation. Consistent with this, Peyrin-Biroulet et al. (2016) showed that patients in HBI-defined clinical remission frequently retain endoscopic activity and that CRP normalisation correlates imperfectly with mucosal healing. Our observation of a clean serum-biomarker gradient across HBI categories, and particularly the steeper gradient for LBP (1.9-fold remission-to-moderate rise, versus 1.19-fold for IL-6) supports the hypothesis that LBP captures persistent subclinical inflammatory activity that symptomatic indices do not fully resolve. Because LBP reflects bacterial translocation rather than purely the epithelial-cytokine axis (Schumann, 2011), its independence from CRP-based acute-phase signals provides complementary — not redundant — information and is plausibly closer to mucosal biology than CRP. Mucosal healing is now a key STRIDE-II treatment target in IBD, associated with reduced surgery, hospitalisation and long-term bowel damage (Turner et al., 2021). In our infliximab-treated subgroup ($n = 35$), patients who achieved mucosal healing had directionally lower IL-23 ($P = 0.073$, trend), LBP, IL-6 and CRP compared with non-healers, although the modest subgroup size precluded formal statistical significance. This pattern mirrors findings from earlier biologic-therapy cohorts, where on-treatment IL-6 reduction correlated with biologic response (Caviglia et al., 2020). It also echoes earlier reports that LBP falls with clinical improvement but less completely in CD than in ulcerative colitis (Pastor Rojo et al., 2007). A quantitatively notable observation is that the IL-23 median was ~20% lower in mucosally-healed patients (65.09 vs 82.03 pg/mL). These patterns, although underpowered statistically, are directionally coherent with the hypothesis that deep remission corresponds to partial normalisation of the IL-23/IL-6 axis, and they provide a quantitative rationale for a prospective biomarker-stratified design in an expanded cohort. Faecal calprotectin, while valuable, requires specialised assay infrastructure and standardised pre-analytical handling that are not routinely

available in many Iraqi hospitals (Dajti et al., 2023; Mohammadi et al., 2017). In this setting, serum biomarkers that can be measured on a standard ELISA microplate reader (IL-23, IL-6, LBP) combined with a fully automated biochemistry analyser (CRP, albumin) offer a practical monitoring panel. The LBP/albumin ratio is especially attractive because it normalises assay variability and integrates nutritional and inflammatory axes in a single simple calculation. Regional IBD guidance — including the 2023 Saudi consensus (Mosli et al., 2023) — currently emphasises CRP and calprotectin, and does not address LBP; our data support extending the biomarker panel to include these candidates for validation. Implementation would require external validation in independent Iraqi cohorts and head-to-head comparison with faecal calprotectin where that is feasible. Previous Iraqi biomarker work in IBD has been relatively sparse. An early Baghdad study by Al-Abassi et al. (2015) measured IL-8, IL-12, IP-10 and IL-10 in Iraqi IBD patients but did not include IL-23 or LBP. Qusay et al. (2024) more recently reported CXCL9 elevation in Iraqi ulcerative colitis, focusing on chemokines rather than acute-phase proteins. In 2025, Abdulla et al. (2025) from Sulaimani reported the diagnostic value of the lymphocyte-to-monocyte ratio in newly diagnosed Iraqi Crohn's disease, highlighting the regional interest in accessible haematological biomarkers. A Karbala study by Abbas (2024) estimated LBP in urinary tract infection patients but did not examine IBD. To the best of our knowledge, the present study is the first Iraqi analysis of IL-23 and LBP stratified by MUST and HBI in Crohn's disease and therefore fills a specific regional knowledge gap. Strengths of this study include: (i) the use of validated clinical instruments (MUST, HBI, Montreal classification, WHO BMI) applied systematically by trained gastroenterologists; (ii) simultaneous measurement of three biologically informative biomarkers (IL-23, IL-6, LBP) alongside CRP and albumin on the same samples, permitting direct comparison on equal methodological footing; (iii) the CD-only stratification design, which avoids the dilution effects of pooling with healthy controls and is therefore sensitive to within-CD variation; (iv) a pre-specified mucosal-healing subgroup analysis; and (v) to our knowledge, the first Iraqi CD cohort reporting serum IL-23 and LBP stratified by nutritional risk and clinical activity. Our study has limitations that must be acknowledged. The cross-sectional design precludes conclusions about the temporal behaviour of biomarkers across MUST or HBI strata or about their ability to predict future deterioration. The single-centre Iraqi setting limits generalisability and requires external validation. The mucosal-healing subgroup (n = 12 vs 23) is underpowered; post-hoc power to detect a 20% reduction in IL-23 at $\alpha = 0.05$ was only 42%, so the directional patterns we observed require confirmation in a larger dataset. We did not measure faecal calprotectin, which would have permitted head-to-head comparison. LBP assay values are not directly numerically comparable with European cohorts because of differences in ELISA platforms and sample dilution protocols; we therefore focus on within-assay relative comparisons and fold changes rather than absolute values. These findings motivate several follow-up studies: (i) prospective longitudinal measurement of IL-23, IL-6 and LBP at baseline and quarterly during biologic maintenance, to test whether changes in biomarkers over time predict deterioration of MUST/HBI status or flare; (ii) validation of the MUST- and HBI-stratified biomarker patterns in independent Iraqi and regional Middle-Eastern cohorts; (iii) prospective enrolment of a larger mucosal-healing cohort (target $n \geq 80$ per group) with paired endoscopy, imaging and biomarker sampling to formally test the IL-23/LBP normalisation hypothesis; (iv) head-to-head evaluation against faecal calprotectin and leucine-rich α2-glycoprotein (Shinzaki et al., 2017); (v) integration of nutritional intervention data; and (vi) mechanistic investigation of single-nucleotide polymorphisms in IL-23R and LBP (Meng et al., 2021) as modifiers of biomarker response.

Conclusion

In this stratified cross-sectional analysis of 67 Iraqi adults with Crohn's disease, serum IL-23, IL-6 and lipopolysaccharide-binding protein rose in a dose–response manner across MUST-defined nutritional-risk and HBI-defined clinical-activity categories, and the LBP/albumin ratio provided the cleanest continuous stratifier within CD patients. CRP and albumin

alone lost sensitivity as within-CD stratifiers compared with their behaviour in a healthy-control comparison. In the infliximab-maintained subgroup, mucosally-healed patients showed directionally lower IL-23, IL-6, LBP and CRP concentrations than non-healers, with the strongest trend for IL-23. These findings support the further evaluation of serum IL-23, IL-6 and LBP as accessible quantitative markers of combined nutritional and inflammatory burden in Crohn's disease, with potential utility in regional settings where endoscopic and faecal-calprotectin monitoring are constrained.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki and local institutional ethical requirements. Ethical approval was obtained from the Ethics Committee of the Ministry of Health, Najaf Health Directorate, Training and Human Development Center (Reference No. 47875, dated 15 December 2025). Written informed consent was obtained from every participant.

Consent for publication

Not applicable.

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Conflicts of Interest

The authors declare no conflict of interest.

Authors' Contributions

AAO and WSH conceived and designed the study. AAO recruited participants, collected clinical data and samples, performed the ELISA and biochemical assays, and drafted the manuscript. WSH supervised laboratory work, interpreted the data, and revised the manuscript critically. Both authors analysed the data, approved the final version and agree to be accountable for all aspects of the work.

Data Availability

The de-identified participant-level dataset supporting the conclusions of this article is available from the corresponding author upon reasonable request and subject to approval by the Ethics Committee of the Faculty of Medicine, University of Kufa.

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