Original Research Article

The Egyptian Journal of Immunology

The Egyptian Journal of Immunology,
E-ISSN (2090-2506)
Volume 33 (1), January, 2026
Pages: 51–61.
www.Ejimmunology.org
https://doi.org/10.55133/eji.330106

Diagnostic value of serum lipocalin-2 in Egyptian patients with inflammatory bowel disease: A case-control study

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Abstract

Inflammatory bowel disease (IBD), encompassing ulcerative colitis (UC) and Crohn's disease (CD), often presents diagnostic challenges. Lipocalin-2 (LCN-2) has emerged as a potential biomarker for intestinal inflammation. This study aimed to evaluate the diagnostic and clinical utility of serum Lipocalin-2 in Egyptian patients with IBD. This was a case-control study, conducted during the period between December 2024 and February 2025, involved 30 IBD patients (18 UC, 12 CD) and 30 age- and sex-matched normal controls. Serum LCN-2 levels were measured using an enzyme linked immunosorbent assay (ELISA). Clinical symptoms, disease activity (via Truelove and Witts' criteria for UC and Harvey-Bradshaw Index for CD), and routine laboratory investigations were assessed. The receiver operating characteristic (ROC) curve analysis was used to assess the diagnostic utility, while Pearson correlation tested associations with clinical and laboratory parameters. IBD patients had significantly elevated serum LCN-2 levels compared to controls (3.15 ± 1.9 vs. 0.24 ± 0.1 ng/mL; $p < 0.001$). The ROC analysis yielded an area under the curve of 0.980, with high sensitivity (96.77%) and negative predictive value (92.31%) at a cutoff of value of 0.22 ng/ml. However, LCN-2 did not significantly differ between UC and CD ($p = 1.000$) or across disease activity levels ($p > 0.05$). Notably, LCN-2 was positively correlated with disease duration ($r = 0.430$, $p = 0.018$) and platelet count ($r = 0.362$, $p = 0.004$), but showed no correlation with hemoglobin, white blood cells, erythrocyte sedimentation rate, creatinine, or glomerular filtration rate. In conclusion, according to our ROC analysis, serum LCN-2 may have an excellent diagnostic utility for identifying IBD but lacks discriminatory power between UC and CD or for assessing disease activity. Its correlation with disease duration and platelet count highlights its potential as a marker of chronic inflammation rather than acute disease severity.

Keywords: IBD; Colitis, UC; CD, LCN-2; NGAL; ELISA.

Date received: 08 September 2025; **accepted:** 12 January 2026

Introduction

Inflammatory Bowel Disease (IBD), comprising Crohn's disease (CD) and ulcerative colitis (UC), results from a complex interplay of genetic predisposition, environmental influences, and gut microbiota dysbiosis.[1-4] These factors contribute to chronic immune-mediated inflammation in susceptible individuals.[1] Globally, IBD affects approximately 6.9 million people, with a higher burden in females. The prevalence is highest in high-income regions such as North America and Europe, reaching up to 429 cases per 100,000 in the United States of America, and 373 per 100,000 in the United Kingdom.[5]

The role of innate immunity particularly neutrophil activity during mucosal inflammation, has gained increasing attention due to being one of the key mechanisms involved in IBD pathogenesis. In this context, lipocalin-2 (LCN-2), a glycoprotein secreted mainly by neutrophils and epithelial cells, emerged as a promising biomarker in microbial infections.[6] LCN-2 limits microbial access to iron by sequestering bacterial siderophores, playing a critical role in host defense.[7] It also contributes to iron homeostasis and affects processes such as cell differentiation and proliferation.[8] Elevated levels of LCN-2 were reported in various inflammatory and neoplastic conditions, including renal injury, infections (e.g. sepsis and pneumonia), and cancer.[8]

Given these properties, the aim of our case-control study was to investigate serum lipocalin-2 as a potential biomarker for IBD. Specifically, we seek to evaluate its diagnostic value in assessing disease activity, offering a potential tool to aid in the non-invasive monitoring and management of IBD.

Materials and Methods

Study Design and Setting

This case-control study was conducted between December 2024 and February 2025 at the Inflammatory Bowel Disease Clinics of the Faculty of Medicine, Ain Shams University, and the National Hepatology and Tropical Medicine Research Institute. The study included two groups. The first included 30 Egyptian patients diagnosed with IBD (cases) while the second group included 30 normal Egyptian individuals as controls. The IBD cases were Egyptian nationals aged between 18 and 65 years, with a glomerular filtration rate (GFR) greater than 90 ml/min, or at least 60 ml/min provided that there were no other signs of kidney disease. Individuals were excluded if they were non-Egyptians, younger than 18 or older than 65 years, or had a GFR below 60 ml/min.

Medical History Assessment

A detailed medical history was obtained from all participants, covering age, sex, place of residence, history of past surgeries (particularly bowel resections) and lifestyle habits such as smoking and alcohol use. For smokers, the smoking index was calculated[9]. Gastrointestinal symptoms such as abdominal pain, diarrhea, rectal bleeding, blood in stool, weight loss, fatigue, fever and anorexia were documented.

Clinical Examination, Anthropometric Assessment, Laboratory Investigations, and Disease Activity Evaluation

Each participant underwent a comprehensive clinical examination to assess general health and identify signs of IBD. Body mass index (BMI) was calculated.[10] In addition, recent weight loss was assessed and categorized as mild (<5%), moderate (5–10%) or severe (>10%) over the past six months.[11] Laboratory investigations which included complete blood count (CBC), serum creatinine and erythrocyte sedimentation rate (ESR) were measured using routine laboratory methods.

Disease activity was assessed using validated indices. For UC, the Truelove and Witts' criteria were used to assess disease severity classified as mild, moderate or severe.[12] For CD, the Harvey-Bradshaw Index (HBI) was applied with disease activity categorized as remission, mild, moderate or severe.[13]

Blood Sampling and Serum Lipocalin-2 Measurement

Venous blood samples were collected from all study participants to assess serum LCN-2 levels.

Sera were separated by centrifugation and stored at -80°C until used. LCN-2 concentrations were measured using commercial Lipocalin-2 ELISA kits (Cat. No. E1429Hu, Bioassay Technology Laboratory, Shanghai, China), according to the manufacturer's instructions. After adding the stop solution, the optical density (OD) was measured using a Microplate reader at 450 nm within 10 minutes.

Statistical Analysis

The sample size was calculated using the statistical software package (STATA, version 10), with 80% power and a 0.05 significance level, yielding 60 participants (30 cases, 30 controls) as adequate for the study. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 20 (SPSS Inc., Chicago, IL, USA). The receiver operating characteristic (ROC) curve analysis was conducted to evaluate the diagnostic performance of the studied parameters.

Results

A total of 60 participants were included in the study. This included 30 patients in the IBD group and 30 controls. The two groups were comparable in terms of demographic characteristics. Additional clinical characteristics are presented in Table 1.

Table 1. Description of Patients' demography across cases and controls.

		Cases		Controls		*p* value
		N	%	N	%	
Total number of participants		30	50.0%	30	50.0%	NS
Age (Years) $_{Mean \pm SD}$ †		34.07 ± 8.32		34.73 ± 8.59		NS
Sex #	Male	15	50.0%	15	50.0%	NS
	Female	15	50.0%	15	50.0%	
HTN ‡	No	28	93.3%	29	96.7%	NS
	Yes	2	6.7%	1	3.3%	
DM ‡	No	28	93.3%	30	100.0%	NS
	Yes	2	6.7%	0	0.0%	
Other comorbidities‡	No	25	83.3%	26	86.7%	NS
	Yes	5	16.7%	4	13.3%	
Smoker ‡	No	27	90.0%	27	90.0%	NS
	Yes	3	10.0%	3	10.0%	
Smoking index (pack years) $_{Mean \pm SD}$ †		12.67 ± 15.31		18.33 ± 12.58		NS
Alcohol	No	30	100.0%	30	100.0%	---
	Yes	0	0.0%	0	0.0%	
Weight (Kg) $_{Mean \pm SD}$ †		74.43 ± 18.27		82.58 ± 17.42		NS
BMI (Kg/m2) $_{Mean \pm SD}$ †		26.37 ± 5.35		29.38 ± 6.58		NS

(#) Chi square test, (‡) Fisher exact test, and (†) Independent t test was used, $p > 0.05$ is not significant (NS).

Abbreviations: HTN: Hypertension. DM: Diabetes mellitus. BMI: Body mass index

Other co-morbidities for the cases include: Atrial fibrillation (1), Vasculitis (1), Multiple sclerosis (1), Primary sclerosing cholangitis (1), Rheumatoid arthritis (1).

Other co-morbidities for control include: Fibromyalgia (1), Hyperthyroidism (1), Kyphoscoliosis (1), Irritable bowel syndrome (1).

Among the 30 patients diagnosed with IBD, 18 (60%) had UC and 12 (40%) had CD. Patients with UC exhibited significantly higher body weight and BMI compared to those with CD (p=0.024 and p=0.028, respectively). Additional demographic details are presented in Table 2.

Table 2. Distribution of Patients' demography among Ulcerative colitis (UC) and Crohn's disease (CD) patients.

		UC		CD		*p* value
		N	%	N	%	
Total number of patients		18	60%	12	40%	NS
Age (years) $_{Mean \pm SD}$ †		33.28 ± 7.61		35.25 ± 9.5		NS
Sex #	Male	10	55.6%	5	10	NS
	Female	8	44.4%	7	8	
HTN ‡	No	17	94.4%	11	17	NS
	Yes	1	5.6%	1	1	
DM ‡	No	17	94.4%	11	17	NS
	Yes	1	5.6%	1	1	
Other Comorbidities	No	16	88.9%	9	75.0%	NS
	Yes	2	11.1%	3	25.0%	
Smoker ‡	No	17	94.4%	10	83.3%	NS
	Yes	1	5.6%	2	16.7%	
Smoking index (Pack years) $_{Mean \pm SD}$ †		1 ±		18.5 ± 16.26		NS
Alcohol	No	18	100.0%	12	100.0%	---
	Yes	0	0.0%	0	0.0%	
Weight (Kg) $_{Mean \pm SD}$ †		80.47 ± 17.02		65.38 ± 16.82		0.024
BMI (Kg/m2) $_{Mean \pm SD}$ †		28.09 ± 4.99		23.79 ± 4.99		0.028
Disease duration since diagnosis (months) $_{Mean \pm SD}$ †		44.89 ± 39.35		21.33 ± 23.07		NS

(#) Chi square test, (‡) Fisher exact test, and (†) Independent t test was used, $p > 0.05$ is not significant (NS).
Abbreviations: HTN: Hypertension. DM: Diabetes mellitus. BMI: Body mass index. CD: Crohn's disease. UC: Ulcerative colitis.
Other co-morbidities for the UC include: Multiple sclerosis (1), Primary sclerosing cholangitis (1)
Other co-morbidities for CD include: Atrial fibrillation (1), Vasculitis (1), Rheumatoid arthritis

Regarding disease activity, none of the UC patients were in remission, whereas two CD patients (16.7%) had achieved remission. Mild disease activity was reported in five patients from each group (27.8% of UC and 41.7% of CD). Moderate activity was the most frequently observed in both groups, seen in 9 UC patients (50.0%) and five CD patients (41.7%). Severe activity was reported in four UC patients (22.2%), while no CD patients were classified as having severe disease. Although some variation in disease activity was observed between the two groups, the difference was not statistically significant ($p = 0.110$).

Description of symptoms and signs

Among the 30 IBD patients and 30 controls, several clinical symptoms and signs showed statistically significant differences. Patients with IBD, compared to controls, had a significantly higher mean pulse rate, bowel movement frequency per day, fatigue, weight loss, abdominal pain, blood in stool, and joint and back pain.

Among IBD patients, fatigue was significantly more common in those with CD (83.3%) compared to those with UC (33.3%) ($p =0.007$). Conversely, the presence of blood in stool was significantly more frequent among UC patients (50%) than CD patients (8.3%) ($p =0.050$).

Laboratory investigations

Regarding laboratory investigations, IBD patients showed several significant differences compared to controls. Hemoglobin levels were significantly lower in the IBD group (mean 11.92 ± 2.48 g/dl) than in controls (13.14 ± 1.95 g/dl, $p = 0.039$). Additionally, the mean corpuscular hemoglobin (MCH) was significantly reduced in cases (25.46 ± 3.49 pg) compared to controls (27.68 ± 2.6 pg, $p = 0.007$). Platelet counts were notably higher in IBD patients (335.17 ± 86.52 × 10^3/µl) than in controls (259 ± 68.58 × 10^3/µl, $p < 0.001$). The most striking finding was a

significantly elevated serum LCN-2 level in IBD patients (3.15 ± 1.9 ng/ml) compared to controls (0.24 ± 0.1 ng/ml, $p < 0.001$), highlighting its potential as a diagnostic biomarker. The remaining laboratory parameters, including the mean corpuscular volume (MCV), red blood cells (RBCs), hematocrit, white blood cells (WBCs), creatinine, GFR, and ESR, showed no statistically significant differences between the two study groups.

Among the key laboratory findings comparing UC and CD patients, UC patients demonstrated significantly higher levels of hemoglobin (12.74 ± 2.26 g/dl vs. 10.7 ± 2.36 g/dl, $p = 0.025$), red blood cells count (4.92 ± 0.77 vs. 4.36 ± 0.63 million/µl, $p = 0.048$), and hematocrit (37.72% ± 5.83 vs. 32.69% ± 6.82, $p = 0.038$). Additionally, CD patients had significantly higher ESR (39.58 ± 31.87 mm/hr vs. 18.89 ± 13.12 mm/hr, $p = 0.020$). Other parameters, including white blood cells count, platelets count, serum creatinine, GFR, and serum LCN-2 levels, did not differ significantly between the two study groups.

Diagnostic Utility and Clinical Correlates of Serum Lipocalin-2 Levels in IBD Patients

Among patients with IBD, serum LCN-2 levels were significantly elevated compared to controls. The mean LCN-2 level in the UC patients was 3.27 ± 2.06 ng/ml, and in CD patients it was 2.96 ± 1.7 ng/ml, while controls had markedly lower levels at 0.24 ± 0.1 ng/ml ($p < 0.001$). Post-hoc analysis confirmed that both UC and CD groups had significantly higher levels than controls ($p < 0.001$ for both), but there was no significant difference between UC and CD patients ($p = 1.000$) (Table 3).

Table 3. Lipocalin-2 level comparison between Ulcerative colitis (UC) patients, Crohn's disease (CD) patients, and controls.

	UC	CD	Control	Overall *p* value
	Mean ± SD (Min – Max)	Mean ± SD (Min – Max)	Mean ± SD (Min – Max)	
Lipocalin-2 (ng/mL)	3.27 ± 2.06 (0.67 - 6.4)	2.96 ± 1.7 (0.19 - 6.4)	0.24 ± 0.1 (0.07 - 0.45)	0.000*

ANOVA test was used, *p-value ≤ 0.05 considered statistically significant.
Post-hoc test was used, between UC and controls (p-value =0.000*), between CD and controls (p-value =0.000*), and between UC and CD (p-value = 1.000).

When assessing the relation between LCN-2 and disease activity, no statistically significant differences were observed across overall IBD activity categories (remission/mild vs moderate/severe; $p = 0.632$), nor within UC ($p = 0.339$) or CD groups ($p = 0.512$). Additionally, LCN-2 levels did not vary significantly between male and female IBD patients ($p = 0.939$) or among patients with different detailed activity scores ($p = 0.266$) (Tables 4-8).

Table 4. Lipocalin-2 level in relation to Overall score among inflammatory bowel disease (IBD) patients.

	Overall score				*p* value
	Remission	Mild	Moderate	Severe	
	Mean ± SD (Min – Max)	Mean ± SD (Min – Max)	Mean ± SD (Min – Max)	Mean ± SD (Min – Max)	
Lipocalin-2 (ng/mL)	1.15 ± 1.36 (0.19 - 2.11)	3.29 ± 2.19 (0.67 - 6.4)	3.59 ± 1.82 (1.65 - 6.4)	2.2 ± 0.95 (1 - 2.98)	NS

ANOVA test was used, $p > 0.05$ is not significant (NS).

Table 5. Lipocalin-2 level in relation to inflammatory bowel disease (IBD) activity among IBD patients.

	IBD activity		*p* value
	Remission & mild	Moderate & severe	
	Mean ± SD (Min – Max)	Mean ± SD (Min – Max)	
Lipocalin-2 (ng/mL)	2.94 ± 2.18 (0.19 - 6.4)	3.28 ± 1.74 (1 - 6.4)	NS

Independent t test was used, $p > 0.05$ is not significant (NS).

Table 6. Lipocalin-2 level in relation to activity among Ulcerative colitis (UC) patients.

	Activity in the UC group		*p* value
	Remission & mild	Moderate & severe	
	Mean ± SD (Min – Max)	Mean ± SD (Min – Max)	
Lipocalin-2 (ng/mL)	2 + 2.39 (0.67 - 6.4)	4 + 1.94 (1 - 6.4)	NS

Independent t test was used, $p > 0.05$ is not significant (NS).

Table 7. Lipocalin-2 level in relation to activity among Crohn's disease (CD) patients.

	Activity in CD group		*p* value
	Remission & mild	Moderate & severe	
	Mean ± SD (Min – Max)	Mean ± SD (Min – Max)	
Lipocalin-2 (ng/mL)	3 + 2.16 (0.19 - 6.4)	3 + 0.81 (1.65 - 3.45)	NS

Independent t test was used, $p > 0.05$ is not significant (NS).

Table 8. Relation between Lipocalin-2 level and gender among inflammatory bowel disease (IBD) patients.

	Sex		*p* value
	Male	Female	
	Mean ± SD (Min – Max)	Mean ± SD (Min – Max)	
Lipocalin-2 (ng/mL)	3.12 ± 2.04 (0.19 - 6.4)	3.17 ± 1.82 (1 - 6.4)	NS

Independent t test was used, $p > 0.05$ is not significant (NS).

Despite the absence of correlation with disease activity severity, LCN-2 demonstrated excellent diagnostic performance in differentiating IBD cases from controls. The area under the ROC curve was 0.980, indicating high overall diagnostic accuracy ($p< 0.001$) (Table 9 and Figure 1). Using a cutoff value of 0.22 ng/ml, LCN-2 showed a sensitivity of 96.77% and a negative predictive value (NPV) of 92.31%, with a negative likelihood ratio of 0.08. However, its specificity was relatively low at 40%, with a positive predictive value (PPV) of 62.48% and a positive likelihood ratio of only 1.61 (Table 10).

Table 9. Area under the curve for Lipocalin-2 level for prediction of inflammatory bowel disease (IBD) (Differentiate between cases and controls).

Test Result Variable(s)	Area Under the Curve	*p* value	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
Lipocalin-2 (ng/mL)	0.980	<0.0001	0.941	1.000

$p \leq 0.05$ is significant.

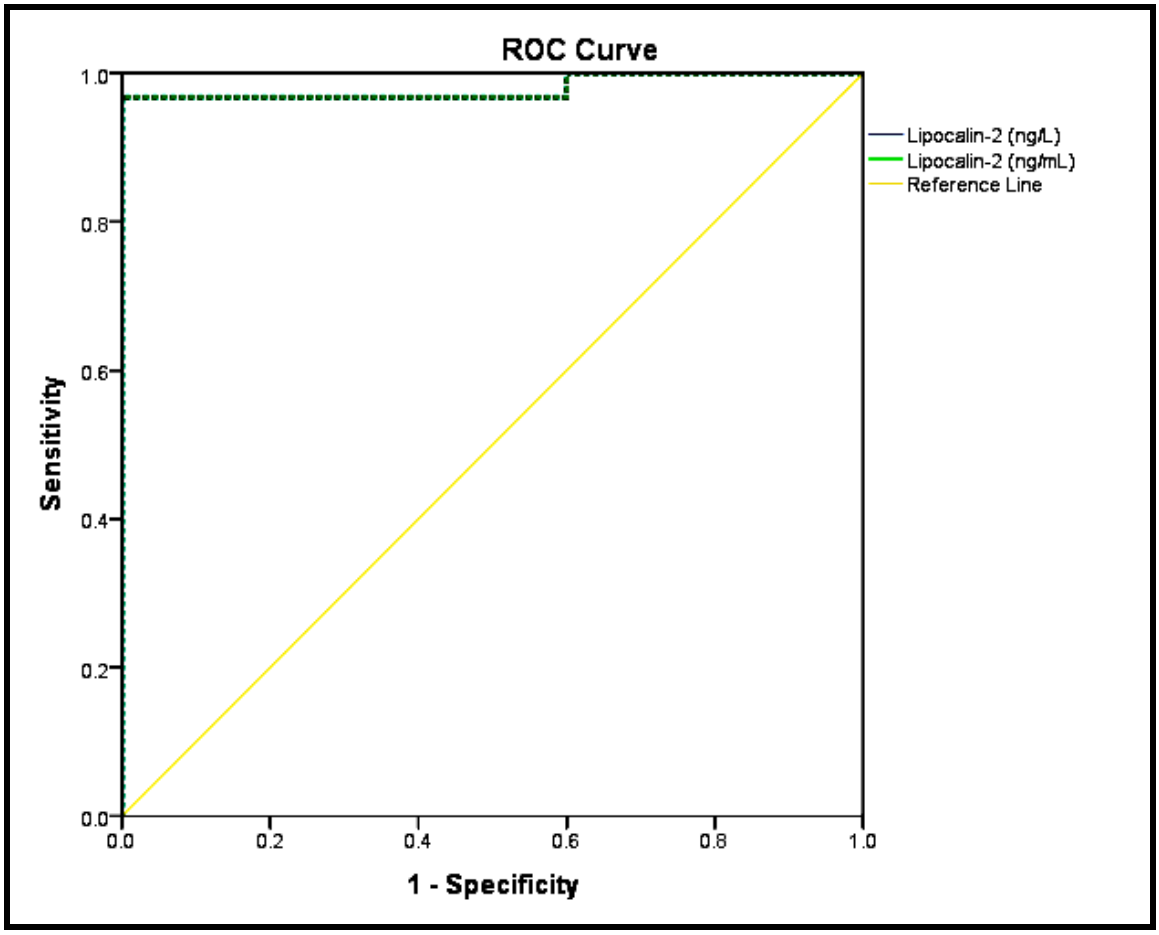

Figure 1. Receiver operating characteristic (ROC) curve for Lipocalin-2 level for prediction of inflammatory bowel disease (IBD) by differentiate between cases and controls.

Table 10. Validity of Lipocalin-2 (at cutoff value of 0.22 ng/ml) for differentiate between cases and controls, and for prediction of inflammatory bowel disease (IBD).

Statistic	Value	95% CI
Sensitivity	96.77%	83.30% to 99.92%
Specificity	40.00%	22.66% to 59.40%
Positive Likelihood Ratio	1.61	1.20 to 2.18
Negative Likelihood Ratio	0.08	0.01 to 0.58
Positive Predictive Value - PPV (*)	62.48%	55.25% to 69.19%
Negative Predictive Value – NPV (*)	92.31%	62.44% to 98.86%
Accuracy (*)	68.84%	55.69% to 80.09%

However, serum LCN-2 levels demonstrated limited diagnostic value when used to distinguish between subtypes of IBD or to predict disease activity. Specifically, the area under the curve (AUC) for differentiating UC from CD was 0.509, indicating no meaningful discriminative power (p = 0.933, 95% CI: 0.297–0.721). Similarly, when assessing the ability of

LCN-2 to predict disease activity across IBD cases, the AUC was only 0.560 (p = 0.626, 95% CI: 0.335–0.786), reflecting poor accuracy.

Lipocalin-2 level in correlation to age, disease duration and laboratory findings among IBD patients

Among IBD patients, serum LCN-2 levels demonstrated a statistically significant positive correlation with both disease duration (r = 0.430, p = 0.018) and platelets count (r = 0.362, p = 0.004). However, no significant correlations were observed between LCN-2 and other laboratory parameters, including hemoglobin, white blood cell count, ESR, creatinine, or GFR. Additionally, there was no correlation between LCN-2 levels and patient age (Table 11).

Table 11. Lipocalin-2 level in correlation to age, disease duration and laboratory findings among inflammatory bowel disease (IBD) patients.

		Lipocalin (2 ng/mL)
Age (Years)	Pearson Correlation	-0.113
	p value	NS
Disease duration since diagnosis (months)	Pearson Correlation	0.430
	p value	0.018
Creatinine (mg/dL)	Pearson Correlation	-0.125
	p value	NS
GFR (mL/min)	Pearson Correlation	0.094
	p value	NS
Hb (g/dL)	Pearson Correlation	-0.068
	p value	NS
MCV (fL)	Pearson Correlation	-0.010
	p value	NS
MCH (pg)	Pearson Correlation	-0.104
	p value	NS
RBCs (10*6/μL)	Pearson Correlation	0.014
	p value	NS
Hct (%)	Pearson Correlation	-0.011
	p value	NS
WBC (10*3/μL)	Pearson Correlation	0.151
	p value	NS
PLT (10*3/μL)	Pearson Correlation	0.362
	p value	0.004
ESR (mm/1st h)	Pearson Correlation	0.226
	p value	NS

(r) Pearson correlation coefficient test was used, $p > 0.05$ is not significant (NS).
Abbreviations: GFR: Glomerular filtration rate. MCV: Mean corpuscular volume. MCH: Mean corpuscular hemoglobin. RBCs: Red blood cells. Hct: Hematocrit. WBC: White blood cells.
PLT: Platelets. ESR: Erythrocyte sedimentation rate.

Discussion

Non-invasive biomarkers represent an emerging research interest, especially in inflammatory bowel disease, as an alternative diagnostic method to endoscopy. This is particularly relevant since endoscopic examinations can be unaffordable or inaccessible for some patients. In this study, we assessed serum LCN-2 as a potential biomarker in IBD patients and investigated whether its level correlates with disease activity in UC and CD disease, using clinical scores such as the Truelove and Witts' criteria and the Harvey-Bradshaw Index, respectively.[12]

Our findings revealed that serum LCN-2 levels were significantly elevated in patients with IBD, with a mean concentration of 3.15 ±

1.9 ng/ml, compared to 0.24 ± 0.1 ng/ml in the control group. Using a cutoff value of 0.22 ng/ml, LCN-2 effectively distinguished IBD cases from controls. These results align closely with those reported in most previous studies exploring the same hypothesis.

However, there are some disagreements in the literature regarding the ability of LCN-2 to differentiate UC from CD. For instance, our study revealed no significant difference in LCN-2 levels between UC patients (3.27 ± 2.06 ng/ml) and CD patients (2.96 ± 1.7 ng/ml). This finding aligns with results from other studies, such as those by Oikonomou et al., 2012, who reported that UC had a mean of 86.62 ± 35.40 ng/ml while CD's mean was 89.92 ± 46.05 ng/ml (p = 0.5949).[14] The study by Budzyńska et al. 2017 also reported the same conclusion with neutrophil gelatinase-associated lipocalin (NGAL) levels: 62.7 ng/ml (45.6 – 90.8 ng/ml) in UC patients versus 60.7 ng/ml (43.9 – 85.2 ng/ml) in CD patients (p = 0.26).[15]

Conversely, the study by El Hagary et al., 2018, reported that LCN-2 levels were significantly higher in active UC with a mean of 90.62 ± 67.87 ng/ml while the mean of active CD was 41.12 ± 8.99 ng/ml (p=0. 0.02).[16]

Another area of debate concerns whether LCN-2 levels correlate with IBD disease activity. This topic was explored using various assessment methods. For example, in 2014 and 2015, De Bruyn et al., reported that LCN-2 correlates with mucosal healing in both UC[17] and CD patients.[18] Similarly, other studies employed clinical activity scores to assess disease activity and correlated them with LCN-2 levels. For example, Oikonomou et al., 2021,[14] Korkmaz et al., 2021[19] and Abozied et al., 2023,[20] each in their respective study used the Clinical Colitis Activity Index for UC and the Crohn's Disease Activity Index for CD. Their studies demonstrated a significant correlation between LCN-2 levels and IBD disease activity. On the other hand, Budzyńska et al., 2017 reported that LCN-2 correlated only with UC disease activity, but not with CD.[15]

In contrast, our analysis did not yield the same conclusion. We found no significant difference in LCN-2 levels among patients in remission (1.15 ± 1.36), and those with mild (3.29 ± 2.19), moderate (3.59 ± 1.82), or severe (2.2 ± 0.95) disease. Additionally, our AUC analysis for disease activity prediction was only 0.560. When we further analyzed UC and CD subtypes separately, we found no significant difference in LCN-2 levels across different clinical activity categories in either disease. Notably, similar findings were reported by Yesil et al., 2013[21] and Nielsen et al., 1999.[22]

Regarding the diagnostic performance of LCN-2, our study showed a sensitivity of 96.7% and a specificity of 40%, with an AUC of 0.980. These values are higher than those reported by Oikonomou et al., 2012, who, at a cutoff $\geq$ 60 ng/ml, found an AUC of 0.722, sensitivity of 76%, and specificity of 59%. However, in active disease, the study by Oikonomou et al., 2012, reported improved values: a cutoff ≥ 75 ng/ml yielded an AUC of 0.93, sensitivity of 95%, and specificity of 83%.[14] Also, the study by Yesil et al., 2013, reported similar diagnostic utility, with an AUC of 0.720, sensitivity of 76.1%, and specificity of 60.9% at a cutoff of 129 ng/ml.[21]

Finally, our study revealed a moderate positive correlation between serum LCN-2 levels and both disease duration (r = 0.430) and platelet count (r = 0.362) ($p \leq 0.05$). However, no significant correlation was found between LCN-2 and WBC (r = 0.151) or ESR (r = 0.226) ($p \geq 0.05$). Notably, these results differ from previous studies. For example, Oikonomou et al., 2012, found a negative correlation between LCN-2 and disease duration (r = - 0.386), as well as a positive correlation with WBC (r = 0.340) in case of UC only. In addition, they found a positive correlation between LCN-2 and ESR in both UC (r = 0.412) and CD (r = 0.354) ($p \leq 0.05$).[14] In contrast, Korkmaz et al., 2021, reported no correlation with disease duration (r=-0,122; $p \geq 0.05$), but they observed significant positive correlations with ESR (r = 0.583) and WBC (r = 0.479) ($p \leq 0.05$).[19]

Our study has several limitations that should be acknowledged. First, the sample size was relatively small. Secondly, we used simpler clinical activity assessment scores, which are routinely applied in our clinical practice, namely, the Truelove and Witts' criteria for UC and the Harvey-Bradshaw Index for CD. Other studies employed more comprehensive scoring

systems, such as the Mayo Score or Clinical Colitis Activity Index for UC and the Crohn's Disease Activity Index for CD.

Additionally, our study focused exclusively on clinical assessment tools and did not incorporate endoscopic findings. This was primarily due to patients being on different treatments like corticosteroids, immunomodulators, and biologics. This economical constraint led to poor compliance with follow-up endoscopy, even during disease flares. Therefore, we could not include the endoscopic assessment in our study even though it's a crucial element.

In conclusion, LCN-2 may serve as a non-invasive biomarker in the diagnosis of IBD. While it appears capable of differentiating IBD patients from normal individuals, it may not effectively distinguish between UC and CD or reflect disease severity. Further studies with larger sample sizes and more robust clinical assessment tools are needed, particularly within the Egyptian population. Such research may help to clarify the prognostic role of lipocalin-2 in disease progression and its potential as a reliable biomarker in clinical practice.

Acknowledgements

The authors would like to thank the participants and staff of the Inflammatory Bowel Disease Clinic at Ain Shams University and the National Hepatology and Tropical Medicine Research Institute. We would also like to thank Dr. Raghda Samir Abdel Latif, Professor of Clinical Pathology in the National Hepatology and Tropical Medicine Research Institute for her continual support during the study.

Author Contributions

MAN; contributed to the study conception and design. MWNA, NAE,, RNMG, MAA, and MAN; contributed to supervision, idea validation, and data collection. NAE, MAA, and MAN; obtained ethical approval from Ain Shams University Hospital and the National Hepatology and Tropical Medicine Research Institute. MEAF; performed the laboratory analysis. MAN; conducted data analysis and wrote the manuscript. All authors contributed to manuscript editing and approved the final version.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) denies receipt of any financial support for the research, authorship, and/or publication of this article.

Ethical approval

The study protocol was reviewed and approved by Research Ethics Committee of the Faculty of Medicine, Ain Shams University (FMASU MS 712/2024) and the National Hepatology and Tropical Medicine Research Institute (ITH00179).

Informed consent

An informed written consent was obtained from each study participant prior to being enrolled in the study..

References

1. Ramos GP, Papadakis KA. (2019). Mechanisms of Disease: Inflammatory Bowel Diseases. *Mayo Clin Proc*. 94(1):155–65.
2. Halfvarson J, Jess T, Magnuson A, et al. (2006). Environmental factors in inflammatory bowel disease: A co-twin control study of a Swedish-Danish twin population. *Inflamm Bowel Dis*. (10):925–33.
3. Orholm M, Munkholm P, Langholz E, et al. (1991). Familial Occurrence of Inflammatory Bowel Disease. *New England Journal of Medicine*. 324(2):84–8.
4. Cleynen I, Boucher G, Jostins L, et al. (2016) Inherited determinants of Crohn's disease and ulcerative colitis phenotypes: A genetic association study. *The Lancet*. ; 387 (10014):156–67.
5. Alatab S, Sepanlou SG, Ikuta K, et al. (2020) The global, regional, and national burden of inflammatory bowel disease in 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Gastroenterol Hepatol*. ;5(1):17–30.
6. Flower DR. (1996) The lipocalin protein family: Structure and function. *Biochemical Journal*; 318(1):1–14.
7. Schmidt-Ott KM, Mori K, Jau YL, et al. (2007). Dual action of neutrophil gelatinase-associated

lipocalin. *Journal of the American Society of Nephrology* ; 18(2):407–13.

8. Ferreira AC, Marques F. (2023). The Effects of Stress on Hippocampal Neurogenesis and Behavior in the Absence of Lipocalin-2. *Int J Mol Sci.*; 24(21):15537.
9. Zhou Y, Hu Y, Yan X, et al. (2023). Smoking index and COPD duration as potential risk factors for development of osteoporosis in patients with non-small cell lung cancer – A retrospective case control study evaluated by CT Hounsfield unit. *Heliyon*. ;9(10).
10. Wu Y, Li D, Vermund SH. (2024). Advantages and Limitations of the Body Mass Index (BMI) to Assess Adult Obesity. *Int J Environ Res Public Health*. ; 21(6).
11. Weir, C. B., & Jan, A. (2023). BMI Classification Percentile and Cut Off Points. *StatPearls*.
12. Truelove SC, Witts LJ. (1995). Cortisone in Ulcerative Colitis. *Br Med J*. ;2 (4947):1041–8.
13. Vermeire S, Schreiber S, Sandborn WJ, et al. (2010). Correlation Between the Crohn's Disease Activity and Harvey-Bradshaw Indices in Assessing Crohn's Disease Severity. *Clinical Gastroenterology and Hepatology*; 8(4):357–63.
14. Oikonomou KA, Kapsoritakis AN, Theodoridou C, et al. (2012). Neutrophil gelatinase-associated lipocalin (NGAL) in inflammatory bowel disease: Association with pathophysiology of inflammation, established markers, and disease activity. *J Gastroenterol*; 47(5):519–30.
15. Budzynska, A., Gawron-Kiszka, Nowakowska-Dulawa, et al. (2017). Serum neutrophil gelatinase-associated lipocalin (NGAL) correlates with clinical and endoscopic activity in ulcerative colitis but fails to predict activity in Crohn's disease. *Journal of physiology and pharmacology: an official journal of the Polish Physiological Society*, *68*(6), 859–865.
16. E El Hagary HM, Mohammed HI, Nooh MA, et al. (2018) Study of serum neutrophil gelatinase-associated lipocalin level in inflammatory bowel disease patients. *Menoufia Medical Journal.* ; 31(2):600–6.
17. De Bruyn M, Arijs I, Wollants WJ, et al. (2014). Neutrophil gelatinase B-associated lipocalin and matrix metalloproteinase-9 complex as a surrogate serum marker of mucosal healing in ulcerative colitis. *Inflamm Bowel Dis.*; 20(7):1198–207.
18. de Bruyn M, Arijs I, De Hertogh G, et al. (2015). Serum Neutrophil Gelatinase B-associated Lipocalin and Matrix Metalloproteinase-9 Complex as a Surrogate Marker for Mucosal Healing in Patients with Crohn's Disease. *J Crohns Colitis*.; 9(12):1079–87.
19. H K, M A, T T, et al. (2021). Evaluation of serum neutrophil gelatinase-associated lipocalin (NGAL), asymmetric dimethylarginine (ADMA) and symmetric dimethylarginine (SDMA) levels, and their relations with disease type and activity in inflammatory bowel diseases. *Turk J Med Sci*.; 51(5).
20. Abozeid F, Ali K, Bahgat M, et al. (2023). Assessing the activity of Inflammatory Bowel Disease using the serum marker: Neutrophil Gelatinase Associated Lipocalin (NGAL). *Mansoura Medical Journal*. ;53(1):2
21. Yeşil A, Gönen C, Şenateş E, et al. (2013). Relationship between Neutrophil gelatinase-associated lipocalin (NGAL) levels and inflammatory bowel disease type and activity. *Dig Dis Sci*. ; 58(9):2587–93.
22. 22. Nielsen OH, Gionchetti P, Ainsworth M, et al. (1999). Rectal dialysate and fecal concentrations of neutrophil gelatinase-associated lipocalin, interleukin-8, and tumor necrosis factor-alpha in ulcerative colitis. *Am J Gastroenterol*.; 94(10):2923–8.