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NESFATINA-1 COMO BIOINDICADOR DE DESREGULAÇÃO METABÓLICA EM DOENÇAS GASTROINTESTINAIS: ANÁLISE DE UM ESTUDO CASO-CONTROLE

NESFATIN-1 AS A BIOINDICATOR OF METABOLIC DYSREGULATION IN GASTROINTESTINAL DISEASES: ANALYSIS OF A CASE–CONTROL STUDY

النيسفاتين-1 كمؤشر حيوي لإختلال التنظيم الأيضي في أمراض الجهاز الهضمي :تحليل دراسة الحالات-الشواهد

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RESUMO

Introdução: A Nesfatina-1 (Nes-1), um peptídeo derivado da nucleobindina-2 (NUCB2), tem sido cada vez mais reconhecida por seu papel na regulação do apetite, do metabolismo da glicose e do equilíbrio lipídico. Evidências crescentes indicam que alterações nos níveis de Nesfatina-1 também podem estar associadas a distúrbios metabólicos relacionados a doenças gastrointestinais (GI). **Objetivo:** Este estudo teve como objetivo investigar os níveis séricos de Nesfatina-1 em pacientes com distúrbios gastrointestinais e avaliar suas associações com parâmetros metabólicos e seu potencial valor diagnóstico. **Métodos:** Estudo de caso-controle conduzido com 128 participantes: 88 pacientes com doenças gastrointestinais e 40 controles aparentemente saudáveis. Os participantes foram recrutados após exame endoscópico no Centro Especializado em Gastroenterologia e Hepatologia, Al-Najaf Al-Ashraf, Iraque, no período de 1º de setembro a 25 de dezembro de 2025. Foram realizadas avaliações laboratoriais incluindo Nesfatina-1 sérica, parâmetros do perfil lipídico (colesterol total, LDL, HDL e triglicerídeos), glicemia, hemoglobina e enzimas hepáticas (ALT e AST). O índice aterogênico do plasma (IAP) foi calculado. As análises estatísticas incluíram estatística descritiva, modelagem de regressão e análise da curva ROC. **Resultados:** Os níveis séricos de Nesfatina-1 foram significativamente menores nos pacientes com doenças gastrointestinais em comparação aos controles saudáveis (11,82 ± 2,19 vs. 20,20 ± 7,14 ng/mL, $p < 0,001$). A análise demonstrou que, à medida que os níveis de Nesfatina-1 diminuíam, o IMC, a glicose, o colesterol total, o LDL, os triglicerídeos e a razão TG/HDL aumentavam. A análise ROC demonstrou elevada eficácia diagnóstica do teste, com área sob a curva (AUC) de 0,91, sendo o melhor ponto de corte de 13,68 ng/mL, com sensibilidade de 80,7% e especificidade de 85,0%. **Discussão:** Esses achados sugerem que a redução dos níveis de Nesfatina-1 pode refletir uma desregulação metabólica subjacente nas doenças gastrointestinais. **Conclusão:** A Nesfatina-1 pode representar um biomarcador promissor para a predição de distúrbios metabólicos e para apoio à avaliação clínica dos distúrbios gastrointestinais.

Palavras-chave: *Nesfatina-1; Doenças gastrointestinais; distúrbios metabólicos; perfil lipídico; índice aterogênico.*

ABSTRACT

Background: Nesfatin-1 (Nes-1), a peptide derived from nucleobindin-2 (NUCB2), has been increasingly recognized for its role in regulating appetite, glucose metabolism, and lipid balance. Growing evidence indicates that alterations in Nesfatin-1 levels may also be linked to metabolic disturbances associated with gastrointestinal (GI) diseases. **Aim**: This study aimed to investigate serum Nesfatin-1 levels in patients with gastrointestinal disorders and to evaluate their associations with metabolic parameters and potential diagnostic value. **Methods**:

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A case-control study was conducted with 128 participants: 88 patients with gastrointestinal diseases and 40 apparently healthy controls. Participants were recruited after endoscopic examination at the Gastroenterology and Hepatology Specialized Center in Al-Najaf Al-Ashraf, Iraq, from September 1 to December 25, 2025. It performed laboratory assessments, including serum Nesfatin-1, lipid profile parameters (total cholesterol, LDL, HDL, and triglycerides), blood glucose, hemoglobin, and liver enzymes (ALT and AST). The atherogenic index of plasma (AIP) was calculated. Statistical analyses included descriptive statistics, regression modeling, and receiver operating characteristic (ROC) curve analysis. **Results**: Serum Nesfatin-1 levels were markedly lower in patients with gastrointestinal diseases than in healthy controls (11.82 ± 2.19 vs. 20.20 ± 7.14 ng/mL, $p < 0.001$). Analysis showed that as Nesfatin-1 levels decreased, BMI, glucose, total cholesterol, LDL, triglycerides, and the TG/HDL ratio increased, ROC analysis showed that the test was very effective at diagnosing, with an area under the curve (AUC) of 0.91, and the best cutoff point was 13.68 ng/mL, achieving a sensitivity of 80.7% and a specificity of 85.0%. **Discussion**: These findings suggest that reduced Nesfatin-1 levels may reflect underlying metabolic dysregulation in gastrointestinal diseases. **Conclusion**: Nesfatin-1 may represent a promising biomarker for predicting metabolic disturbances and supporting the clinical evaluation of gastrointestinal disorders.

Keywords: *Nesfatin-1; Gastrointestinal diseases; metabolic disturbances; lipid profile; and atherogenic index.*

الملخص

الخلفية: يُعدّ النيسفاتين-1(Nes-1)، وهو ببتيد مشتق من النيوكليوبيندين-2 (NUCB2)، من الجزيئات التي حظيت باهتمام متزايد لدوره في تنظيم الشهية واستقلاب الغلوكوز وتوازن الدهون. وتشير الأدلة المتزايدة إلى أن التغيرات في مستويات نيسفاتين-1 قد ترتبط أيضًا بالاضطرابات الأيضية المصاحبة لأمراض الجهاز الهضمي. **الهدف**: هدفت هذه الدراسة إلى تقصّي مستويات نيسفاتين-1 في مصل الدم لدى المرضى المصابين باضطرابات الجهاز الهضمي، وتقييم علاقتها بالمعلمات الأيضية وقيمتها التشخيصية المحتملة. **طرائق العمل**: أُجريت دراسة حالة–شاهد شملت 128 مشاركًا: 88 مريضًا يعانون من أمراض الجهاز الهضمي و40 شخصًا سليمًا ظاهريًا كمجموعة ضابطة. وتم اختيار المشاركين بعد إجراء الفحص التنظيري في مركز أمراض الجهاز الهضمي والكبد التخصصي في النجف الأشرف، العراق، خلال الفترة من 1 أيلول إلى 25 كانون الأول 2025. وقد أُجريت تحاليل مخبرية شملت قياس نيسفاتين-1 في المصل، ومعلمات الملف الدهني (الكوليسترول الكلي، LDL، HDL، والدهون الثلاثية)، وسكر الدم، والهيموغلوبين، وإنزيمات الكبد (ALT وAST). كما تم حساب مؤشر التصلب العصيدي في البلازما (AIP). وشملت التحليلات الإحصائية الإحصاء الوصفي، ونمذجة الانحدار، وتحليل منحنى الخصائص التشغيلية للمستقبِل (ROC).**النتائج**: كانت مستويات نيسفاتين-1 في المصل أقل بشكل ملحوظ لدى المرضى المصابين بأمراض الجهاز الهضمي مقارنةً بالأشخاص الأصحاء (11.82 ± 2.19 مقابل 20.20 ± 7.14 نانوغرام/مل، $p < 0.001$). وأظهر التحليل أنه مع انخفاض مستويات نيسفاتين-1 ترتفع قيم مؤشر كتلة الجسم (BMI)، والغلوكوز، والكوليسترول الكلي، وLDL، والدهون الثلاثية، ونسبة TG/HDL. كما أظهر تحليل ROC أن الاختبار يتمتع بفعالية عالية في التشخيص، حيث بلغت المساحة تحت المنحنى (AUC) 0.91، وكانت أفضل نقطة قطع 13.68 نانوغرام/مل، مع حساسية بلغت 80.7% ونوعية بلغت 85.0%. **المناقشة**: تشير هذه النتائج إلى أن انخفاض مستويات نيسفاتين-1 قد يعكس وجود خلل في التنظيم الأيضي لدى مرضى الجهاز الهضمي. **الاستنتاج**: قد يمثّل نيسفاتين-1 مؤشرًا حيويًا واعدًا للتنبؤ بالاضطرابات الأيضية ودعم التقييم السريري لاضطرابات الجهاز الهضمي.

الكلمات المفتاحية: النيسفاتين-1؛ أمراض الجهاز الهضمي؛ الاضطرابات الأيضية؛ الملف الدهني؛ المؤشر التصلبي الوعائي.

1. INTRODUCTION:

Gastrointestinal (GI) diseases are a significant global health issue, frequently associated with metabolic disorders that may influence disease progression and treatment efficacy. In recent years, there has been growing interest in regulatory peptides that link the physiology of the gastrointestinal system to the body's overall metabolic balance. Nesfatin-1 (Nes-1) is a bioactive peptide that comes from nucleobindin-2 (NUCB2). It is now an important regulator of metabolic function and energy balance (Schalla & Stengel, 2019).

Researchers first identified nesfatin-1 in the hypothalamus, where it helps regulate hunger and energy levels. Later research showed that this peptide is present throughout the body, not just in the central nervous system. It can also be found in the pancreas, stomach, fat tissue, and intestinal mucosa (Stengel & Taché, 2021). Nesfatin-1 is found in many different tissues, suggesting it does more than control hunger. It is very important for controlling metabolism and how the digestive system works.

There is growing evidence that nesfatin-1 helps stabilize blood sugar levels and aid fat breakdown. Nesfatin-1 can alter insulin secretion, glucose utilization, and lipid breakdown. This suggests it may be involved in metabolic disorders such as obesity, insulin resistance, and dyslipidemia (Aydin, 2021; Schalla *et al*., 2021). Changes in circulating nesfatin-1 levels have also been linked to several metabolic disorders. This suggests that this peptide may be a sign of metabolic imbalance (Algul *et al*., 2020).

New studies show that nesfatin-1 may also affect the digestive system, not just metabolism. Previous studies have shown that nesfatin-1 can alter gastric motility, the body's response to inflammation, and communication

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between the gut and brain (Li *et al*., 2022). These results suggest that nesfatin-1 may be involved in the complicated link between metabolic control and gastrointestinal disease.

There is increasing evidence about how nesfatin-1 works in the body, but few clinical studies have examined its effects on gastrointestinal diseases. It's not at all clear how changes in metabolism in people with GI disorders are linked to blood nesfatin-1 levels. Learning more about this link could reveal how metabolic processes work in people with gastrointestinal diseases and help us identify new biomarkers for diagnosis.

1.1. Aims

Consequently, the present study aimed to evaluate serum nesfatin-1 concentrations in patients with gastrointestinal disorders and to investigate their association with metabolic parameters, including lipid profiles and glucose levels. This study also sought to examine how well nesfatin-1 could distinguish between patients with gastrointestinal disorders and healthy controls.

2. MATERIALS AND METHODS:

2.1. Material

2.1.1. Study Design and Population

This case–control study was performed from September to December 2025 at Gastroenterology and Hepatology Specialized Center in Al-Najaf Al-Ashraf, Iraq. The study included 128 participants aged 15 to 70. All participants underwent upper gastrointestinal endoscopy, a procedure that involves inserting a flexible endoscope with a camera through the mouth to visualize the esophagus, stomach, and duodenum for diagnostic purposes. Based on clinical and endoscopic findings, participants were divided into two groups: 88 patients with gastrointestinal diseases and 40 apparently healthy individuals who constituted the control group. Demographic and clinical data were collected through standardized questionnaires and medical record review. These data encompassed age, sex, body mass index (BMI), smoking status, and pertinent clinical history. Participants with a history of chronic liver disease, renal disease, autoimmune disorders, metabolic diseases, malignancy, prior gastric surgery, or those undergoing medications that could affect metabolic parameters were excluded from the study.

The sample size was determined based on the availability of qualified participants during the study period and in alignment with analogous previously published research on nesfatin-1 levels in clinical populations.

2.2. Methods

2.2.1. Body Mass Index (BMI)

The computation of BMI is performed by a balance and height device, for calculating the weight and height, and applying Equation 1, to measure body mass index (BMI), calculated as weight in kilograms divided by the square of height in meters (kg/m^2) (Feng *et al*., 2019).

BMI = weight (kg) / Height (m^2) (Eq.1)

2.2.2. Blood Sample Collection

Under sterile conditions, about 5 mL of venous blood was taken from each participant. The blood samples were allowed to clot and then spun at 3000 rpm for 10 minutes to separate the serum. We kept the serum samples at −20 °C until we could perform additional biochemical tests.

2.2.3. Determination of Serum Nesfatin-1

Serum Nesfatin-1 (Nes-1) concentrations were determined using a commercial Human Nesfatin-1 ELISA kit supplied by BT LAB, China (Cat. No. E3063Hu) according to the manufacturer's instructions. The assay is based on the sandwich enzyme-linked immunosorbent assay (ELISA) technique. Microplate wells are pre-coated with antibodies specific for human Nesfatin-1. Serum samples are added to the wells, allowing Nesfatin-1 present in the samples to bind to the immobilized antibodies. A biotin-labeled anti-Nesfatin-1 antibody is then added, followed by streptavidin-horseradish peroxidase (HRP). After incubation and washing steps, the substrate solution is added, resulting in a color reaction proportional to the concentration of Nesfatin-1 in the sample.

The assay has a standard curve range of 0.3–90 ng/mL and a sensitivity of 0.15 ng/mL. According to the manufacturer, the assay demonstrated acceptable precision with an intra-

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assay coefficient of variation (CV) < 8% and inter-assay CV < 10%.

2.2.4. Biochemical Measurements

Biochemical parameters were analyzed using the Cobas c111 clinical chemistry analyzer (Roche Diagnostics). The following parameters were measured: Total cholesterol (TC), Triglycerides (TG), High-density lipoprotein cholesterol (HDL-C), Alanine aminotransferase (ALT), and Aspartate aminotransferase (AST).

Specific Roche diagnostic reagents were used, including ALT (Cat. No. 20764911) and AST (Cat. No. 20764920). Quality control was performed using PreciControl ClinChem Multi 1 and Multi 2 together with Calibrator f.a.s. (Roche Diagnostics) to ensure analytical accuracy and reliability. Low-density lipoprotein cholesterol (LDL-C) and very-low-density lipoprotein cholesterol (VLDL-C) were calculated using the Friedewald equation (Equations 2 and 3). Lipid concentrations were initially calculated in mg/dL and subsequently converted to mmol/L for the lipid profile.

[Analyte] (mg/dl) = (Absorbance of Sample/ Absorbance of Standard) ×[Standard] (mg/dl (Eq.2)

[LDL-C] (mg/dl) = [Total Cholesterol] - ([Triglycerides] / 5) - [HDL Cholesterol]; [VLDL-C] (mg/dl) = [Triglycerides] / 5 (Eq.3)

2.2.5. Random Blood Glucose Measurements

Random blood glucose (RBG) levels were measured in serum samples using an automated biochemical analyzer (Cobas c111, Roche Diagnostics), according to the manufacturer's standard procedures. The method is based on the enzymatic colorimetric glucose oxidase technique, which allows quantitative determination of glucose concentration in blood samples. Quality control procedures were performed regularly using standard calibration materials to ensure the accuracy and reliability of the measurements.

2.2.6. Calculation of Atherogenic Index of Plasma

The atherogenic index of plasma (AIP) was calculated to evaluate the atherogenic risk associated with lipid metabolism. AIP was determined using the logarithmic transformation of the ratio between triglycerides and high-density lipoprotein cholesterol according to Equation 4.

AIP = log10 (Triglycerides / HDL-C) (Eq.4)

where triglycerides and HDL-C are expressed in mmol/L.

2.2.7. Investigation of Helicobacter pylori

The assessment of Helicobacter pylori (H. pylori) infection was conducted using two diagnostic techniques: the urea breath test and the stool antigen test, each selected to provide complementary diagnostic accuracy. In the urea breath test, the Heliprobe® system (manufactured in Sweden) was used to detect H. pylori infection by measuring urease activity. Participants were instructed to fast for 6 to 7 hours prior to the procedure to ensure optimal test sensitivity. Initially, a baseline breath sample was obtained by having the patient exhale into a balloon-like container or tube. Subsequently, the patient ingested a urea solution labeled with a carbon isotope, either radioactive or non-radioactive, designed to react with urease produced by H. pylori. After a 10–30-minute wait, a second breath sample was collected. The two breath samples were then analyzed and compared to detect the presence of labeled carbon dioxide, indicative of urease-mediated urea hydrolysis by H. pylori. This stepwise approach enabled precise detection of H. pylori infection with high sensitivity and specificity.

For the stool antigen test, stool samples were collected and analyzed by an enzymatic immunoassay using a commercial diagnostic kit specifically developed for H. pylori antigen detection. The enzyme immunoassay utilized monoclonal antibodies to identify H. pylori antigens, providing a non-invasive diagnostic alternative that complements the urea breath test. The combined use of both diagnostic methods was intended to enhance overall diagnostic accuracy and mitigate the risk of false-negative results, thereby ensuring a more comprehensive assessment of H. pylori infection status.

2.3. Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS), version 27. Continuous variables were expressed as mean ± standard deviation (SD), whereas categorical variables were presented as

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frequencies and percentages when appropriate. The normality of the data distribution was evaluated using Q–Q plots. Differences between study groups were analyzed using appropriate statistical tests for quantitative variables. The relationship between serum Nesfatin-1 and metabolic parameters was assessed using multiple linear regression analysis.

Furthermore, receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic performance of serum Nesfatin-1 in distinguishing patients with gastrointestinal diseases from healthy controls. The area under the curve (AUC), sensitivity, specificity, and optimal cutoff value were determined. A p-value < 0.05 was considered statistically significant.

The effect size for the primary outcome (serum Nesfatin-1) was calculated using Cohen's d. The observed effect size was large (Cohen's d = 1.92), indicating that the sample was adequate to detect the between-group difference with high precision

3. RESULTS AND DISCUSSION:

3.1. Results

3.1.1. Baseline Characteristics of the Study Population

The statistical analysis compares GI patients to healthy controls in Table 1. There was no significant difference in age (36.81 ± 13.88 vs. 35.38 ± 10.78 years, p = 0.564), age groups (>35, 25–34, 15–24; p = 0.602), or sex distribution (p = 0.088). GI patients had a higher BMI (26.25 ± 3.45 vs. 24.90 ± 2.95, p = 0.026) and a higher proportion were classified as overweight or obese. Fasting glucose levels were higher in GI patients (106.62 ± 21.43 vs. 91.38 ± 9.66 mg/dL, p < 0.001), while hemoglobin levels were lower (11.75 ± 1.57 vs. 12.71 ± 1.16 g/dL, p < 0.001), and there were more cases of moderate and mild anemia (p = 0.052). In GI patients, liver enzymes ALT and AST were slightly lower (ALT: 12.68 ± 6.06 vs. 14.91 ± 5.35 U/L, p = 0.040; AST: 16.92 ± 5.20 vs. 18.97 ± 5.45 U/L, p = 0.049). However, total serum bilirubin did not differ significantly (p = 0.376). A lipid profile analysis showed that GI patients had higher triglycerides (2.13 ± 0.58 vs. 1.42 ± 0.37 mmol/L, p < 0.001) and TG/HDL ratios (1.87 ± 0.76 vs. 1.06 ± 0.38, p < 0.001) but lower HDL (1.21 ± 0.20 vs. 1.37 ± 0.18 mmol/L, p < 0.001). Total cholesterol and LDL levels were not significantly different. The atherogenic index of plasma (AIP) showed that more GI patients were at moderate to high risk (39.8% vs. 7.5%, p < 0.001). Nes-1 levels were markedly diminished in GI patients (11.82 ± 2.19 vs. 20.20 ± 7.14, p < 0.001). Regarding medication, 39.8% of GI patients were receiving treatment for their primary diagnosis or biological therapy, whereas none of the controls received any medication (p = 0.037).

3.1.2. Distribution and comparative concentrations of serum Nesfatin-1

Figure 1 shows the distribution of serum Nesfatin-1 (Nes-1) levels and their comparison between patients with gastrointestinal (GI) diseases and healthy controls.

The Q–Q plots in Figures 1A and 1B show the distribution of Nes-1 values across the two study groups. This is how we check for normality. In patients with GI (Figure 1A), the data points are very close to the reference diagonal line. This shows that the observed values are mostly in line with a normal distribution, with only small differences at the extreme values. The control group (Figure 1B) also shows a roughly linear pattern along the reference line, with small changes at the lower and upper tails of the distribution. In general, the plots show that the Nes-1 values in both groups are distributed close to normal.

Figure 1C shows that the mean serum Nes-1 level in patients with gastrointestinal diseases was 11.82 ± 2.19 ng/mL. In contrast, the control group had a higher mean value of 20.20 ± 7.14 ng/mL. Statistical analysis showed that the difference between the two groups was very significant (P < 0.001).

3.1.3. Distribution of Subdiagnosis of Gastrointestinal Disease and Associated Nesfatin-1 Levels

The results in Figure 2 show how the different types of gastrointestinal (GI) diseases are distributed among patients and how much Nesfatin-1 (Nes-1) is in their blood. Organic gastrointestinal disorders accounted for the majority of cases (69 patients, 78%), while functional disorders accounted for 19 patients (22%), indicating a statistically significant predominance of organic conditions ($\chi^2 = 28.41$, P < 0.001), as shown in Figure 2A.

Figure 2B's statistical analysis showed a very big difference in Nes-1 levels between the study groups (P < 0.001). The primary factor

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contributing to this difference was the significantly elevated Nes-1 levels in the healthy control group compared to all gastrointestinal disease categories. In contrast, the patient groups displayed relatively uniform concentrations within a narrow range (approximately 10–12 ng/mL).

Irritable bowel syndrome (IBS) was the most common diagnosis, accounting for 22% of cases (n = 19). IBS patients, despite being the most common diagnosis, showed a moderate drop in Nes-1 levels, with a mean concentration of 12.17 ± 2.22 ng/mL compared to the healthy control group (20.20 ± 7.14 ng/mL).

The second most common condition was Helicobacter pylori–associated gastritis (20%, n = 18), with patients having a mean Nes-1 level of 12.22 ± 2.19 ng/mL, indicating that their circulating Nes-1 levels were similar to those of healthy people. Ulcerative colitis, which accounted for 19% of the cases (n = 17), had a mean concentration of 11.95 ± 2.29 ng/mL, slightly lower than that of the other cases.

Crohn's disease, comprising 13% of the cohort (n = 11), had the lowest mean Nes-1 level among all gastrointestinal disease groups (10.08 ± 1.46 ng/mL), suggesting a greater reduction in circulating Nes-1 in this inflammatory bowel disease subtype. Conversely, celiac disease, representing 11% of the patient cohort (n = 10), exhibited a mean Nes-1 level of 12.39 ± 2.34 ng/mL, which is consistent with levels found in other non-ulcerative gastrointestinal disorders.

Gastric ulcer (6%, n = 5) and GERD with gastritis (6%, n = 5) were less common, with mean Nes-1 concentrations of 10.31 ± 1.23 ng/mL and 11.38 ± 1.03 ng/mL, respectively. Small intestinal ulcer, constituting the smallest proportion of cases (3%, n = 3), exhibited a comparatively elevated mean Nes-1 level (14.03 ± 2.50 ng/mL) relative to other gastrointestinal diseases.

3.1.3. Linear Regression Analysis of Factors Associated with Nesfatin-1 Levels

The current study used multiple linear regression to examine the association between serum Nesfatin-1 (Nes-1) levels and various clinical and biochemical factors in individuals with gastrointestinal diseases (Table 2). Figure 4's scatterplot shows the overall regression relationship between standardized predicted values and observed Nes-1 concentrations.

The study found that body mass index (BMI) was strongly and negatively linked to Nes-1 levels (B = −0.26, β = −0.41, p = 0.005). This means that people with higher BMI tended to have lower levels of Nes-1 in their blood.

There was a very strong negative relationship between fasting glucose and Nes-1 (B = −0.07, β = −0.73, p < 0.001). This suggests that higher glucose levels are strongly linked to lower Nes-1 levels.

Similarly, several lipid profile parameters showed significant negative correlations with Nes-1. These included total cholesterol (TC) (B = −0.90, β = −0.37, p < 0.001), low-density lipoprotein cholesterol (LDL-C) (B = −1.01, β = −0.40, p < 0.001), triglycerides (TG) (B = −0.90, β = −0.24, p = 0.024), and the TG/HDL ratio (B = −0.75, β = −0.26, p = 0.013). These results show that higher levels of atherogenic lipids are linked to lower levels of Nes-1.

On the other hand, high-density lipoprotein cholesterol (HDL-C) was strongly associated with Nes-1 (B = 3.04, β = 0.28, p = 0.009), suggesting that higher HDL levels may be associated with higher Nes-1 levels in the blood.

However, there were no statistically significant links between age (p = 0.282), hemoglobin (p = 0.086), ALT (p = 0.660), AST (p = 0.972), or total serum bilirubin (p = 0.385) and Nes-1 levels.

Figure 3 shows a scatterplot of the linear relationship between standardized predicted values and serum Nesfatin-1 (Nes-1) levels in patients with gastrointestinal diseases. Each point represents a different patient. The fitted linear model shown by the red regression line is y = 11.82 + 1.74x. This indicates a positive linear relationship between the predicted regression values and the measured Nes-1 levels.

3.1.4. Diagnostic Performance of Nesfatin-1 Based on ROC Curve Analysis

Receiver operating characteristic (ROC) curve analysis (Figure 4) was conducted to assess the diagnostic performance of serum Nesfatin-1 (Nes-1) in differentiating patients with gastrointestinal (GI) diseases from healthy controls. The analysis demonstrated that Nes-1 possesses excellent discriminatory capacity, with an area under the curve (AUC) of 0.91 (95% confidence interval: 0.85–0.96, p < 0.001).

The optimal cutoff value for Nes-1 was determined to be 13.68 ng/mL, based on the

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maximum Kolmogorov–Smirnov statistic, which identifies the point of greatest separation between patient and control distributions. At this threshold, Nes-1 achieved a sensitivity of 80.7% and a specificity of 85.0%.

3.2. Discussion

The current study demonstrates that patients with gastrointestinal (GI) diseases exhibited significantly reduced circulating nesfatin-1 levels compared to healthy controls, accompanied by a metabolic profile characterized by elevated BMI, increased fasting glucose, heightened triglycerides, an elevated TG/HDL ratio, and diminished HDL levels. When taken together, these results point to a gut–metabolic axis rather than a local intestinal event. This interpretation is biologically plausible because nesfatin-1 is not only a central anorexigenic peptide but is also expressed in peripheral tissues, including the gastric mucosa, pancreas, adipose tissue, and other components of the digestive system. Recent reviews consistently characterize nesfatin-1 as a multifunctional regulator of appetite, glucose metabolism, lipid metabolism, oxidative stress, and inflammatory signaling, rendering it pertinent to heterogeneous gastrointestinal cohorts, including the one examined in this study (Damian-Buda *et al*., 2024; Dore *et al*., 2017; Gonkowski *et al*., 2022; Schalla & Stengel, 2018; Stengel & Taché, 2011).

From a mechanistic standpoint, the regression results align with the experimental literature. Nesfatin-1 was initially characterized as a satiety-related NUCB2-derived peptide in the hypothalamus (Oh-I *et al*., 2006); subsequent research, however, has demonstrated that its effects extend significantly beyond appetite regulation. Experimental studies have shown that nesfatin-1 can directly increase glucose-dependent insulin secretion in β-cells, make insulin more effective, change how the liver makes glucose, and change how insulin-target tissues take up glucose (Gonzalez *et al*., 2011; Li *et al*., 2013; Wu *et al*., 2014; Geng *et al*., 2025). This establishes a robust biological foundation for the observation that reduced nesfatin-1 levels correlate with elevated fasting glucose levels and less favorable metabolic indices. Instead of being a single peptide change, lower levels of nesfatin-1 in the GI group may be a sign of problems in a larger endocrine network that connects nutrient sensing, intestinal signaling, insulin response, and liver metabolism (Geng *et al*., 2025).

The current lipid results are just as important. The negative correlations between nesfatin-1 and total cholesterol, LDL, triglycerides, and the TG/HDL ratio, along with the positive correlation with HDL, align with the increasing body of literature linking nesfatin-1 to lipid metabolism and cardiometabolic risk. Reviews and mechanistic studies demonstrate that nesfatin-1 is involved in hepatic lipid regulation, adipocyte biology, and systemic lipid homeostasis (Luo *et al*., 2021; Dore *et al*., 2017). This indicates that the diminished nesfatin-1 observed in GI patients may not solely reflect disease burden; it may also delineate a subgroup exhibiting a more atherogenic metabolic phenotype. AIP findings, along with the fact that the GI patients in the cohort were more metabolically unfavorable than controls, even though the age and sex distributions were similar, support that interpretation. In terms of the thesis, this is a strong point: the peptide is not only lower in disease, but it also has a biologically coherent metabolic profile that goes along with it.

Simultaneously, the clinical literature regarding circulating nesfatin-1 is not entirely consistent; some studies have found that nesfatin-1 levels were lower in people with higher BMI or metabolic problems. For example, in non-obese men, there was an inverse relationship with BMI, and in overweight patients, there was a predictive relationship with metabolic syndrome (Tsuchiya *et al*., 2010; Alsarraf *et al*., 2025). Other research has reported elevated levels of circulating nesfatin-1 in newly diagnosed type 2 diabetes or in specific obesity-related contexts (Zhang *et al*., 2012; Ramanjaneya *et al*., 2010). This variability indicates that serum nesfatin-1 is context-dependent and may fluctuate based on adiposity compartment, disease stage, medication status, inflammatory tone, assay platform, and whether the cohort is primarily metabolic, inflammatory, or mixed. The most defensible conclusion for this dataset is not that nesfatin-1 is present in every disorder, but that in this heterogeneous GI population, it correlated with an adverse metabolic state and distinctly differentiated patients from controls.

Another significant aspect of the present findings is that nesfatin-1 levels were diminished across gastrointestinal subdiagnoses, exhibiting only minor variations among the disease categories. This pattern contradicts a strictly disease-specific interpretation and supports the notion that nesfatin-1 signifies a common pathophysiological disturbance among gastrointestinal disorders. Recent reviews of

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digestive diseases support that view by placing nesfatin-1 at the crossroads of inflammatory signaling, oxidative balance, mucosal regulation, and metabolic control (Damian-Buda *et al*., 2024). Studies indicating the involvement of nesfatin-1 in gut physiology, gastric function, and brain–gut stress signaling provide further support (Gonkowski *et al*., 2022; Yang *et al*., 2017; Stengel & Taché, 2011). Consequently, the uniformity of reduction across GI subgroups may suggest that the prevailing signal is not "Crohn's vs ulcer vs IBS," but rather "GI disease with systemic metabolic strain" versus health.

These findings regarding peptic ulcers are also relevant in a broader clinical context. A recent review in JAMA confirms that peptic ulcer disease is still strongly linked to H. pylori, NSAID exposure, and clinically important complications. The additional Iraqi study suggests that ulcer patients may have both biochemical and metabolic problems simultaneously (Vakil, 2024; Abd-Alameer & Sharba, 2025). This does not demonstrate that dyslipidemia or altered nesfatin-1 induces ulcer disease; however, it substantiates the overarching assertion that gastrointestinal disorders frequently coexist with systemic biochemical disturbances. Nesfatin-1 may function less as a specific "GI lesion marker" and more as a biomarker of the metabolic-inflammatory environment associated with GI disease.

Lastly, the ROC analysis demonstrated a robust discriminatory capacity of serum Nesfatin-1 in differentiating gastrointestinal patients from healthy controls (AUC = 0.91). This discovery indicates that Nesfatin-1 could serve as a potential biomarker linked to metabolic changes in gastrointestinal disorders. However, as the results were derived from a single case–control dataset, additional validation in larger, more heterogeneous populations is necessary before affirming its clinical applicability.

4. CONCLUSIONS:

The current study found that patients with gastrointestinal diseases had significantly lower serum Nesfatin-1 levels than healthy controls. The distribution analysis showed that Nesfatin-1 values were roughly normally distributed in both groups. This supports the accuracy of the statistical comparisons. The ROC curve analysis also showed that Nesfatin-1 was very effective at distinguishing healthy individuals from those with gastrointestinal problems, with an area under the curve (AUC) of 0.91. The cutoff value of 13.68 ng/mL showed good sensitivity (80.7%) and specificity (85.0%), indicating it was effective at distinguishing between the two groups.

In general, these results indicate that people with gastrointestinal disorders have much lower serum Nesfatin-1 levels. This could be a useful biomarker for distinguishing between sick and healthy people.

5. DECLARATIONS

5.1. Study Limitations

The study had several limitations that should be considered when interpreting the findings. This study has several limitations that should be acknowledged. First, the study was conducted at a single medical center, which may limit the generalizability of the findings to broader populations. Second, although the sample size was determined based on participant availability during the study period, the observed effect size for the primary outcome was large (Cohen's d = 1.92), suggesting that the sample was sufficient to detect the main between-group difference. Nevertheless, a formal a priori sample size calculation was not performed, and future studies should include pre-specified power calculations to strengthen the methodological rigor. Third, the case–control design limits the ability to establish causal relationships between Nesfatin-1 levels and metabolic alterations in gastrointestinal diseases. Additionally, the study evaluated serum Nesfatin-1 at a single time point, which may not fully reflect potential dynamic changes over time. Future studies involving larger multicenter cohorts and longitudinal designs are recommended to further validate these findings and clarify the role of Nesfatin-1 in gastrointestinal disease–related metabolic dysregulation.

5.2. Acknowledgements

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5.3. Funding source

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5.4. Competing Interests

The authors declare that they have no competing interests or conflicts of interest that could have influenced the work presented in this manuscript. This includes, but is not limited to, financial relationships, personal affiliations, intellectual property considerations, or other potential sources of bias. All authors have reviewed and approved this declaration, ensuring transparency and maintaining scientific integrity in the reporting of this research.

5.5. Data Availability

All data presented in this study are available in the manuscript tables and figures. Raw data are available upon request from the corresponding author.

5.6. Author Contributions

Swar Adnan Mohammed (SAM): Collected data (DC), contributed to manuscript writing (MW), and approved the final version of the manuscript (FA). Intisar Razzaq Sharba (IRS): Led the conception and design of the study (CD), performed data analysis and interpretation (DAI), contributed to manuscript writing (MW), conducted critical review (CR), and approved the final version of the manuscript (FA). Jinan Mohammed Zahid (JMZ): Contributed to the conception and design of the study (CD), participated in manuscript writing (MW), conducted critical review (CR), and approved the final version of the manuscript (FA).

5.7. AI and Computational Tools Declaration

The authors declare that artificial intelligence (AI) tools were used solely for minor language editing to improve grammar, sentence structure, and overall clarity of the manuscript. AI was not used in the design of the study, data collection, statistical analysis, interpretation of the results, or in generating the scientific conclusions. All scientific content, analyses, and interpretations presented in this work are the responsibility of the authors.

5.8. Research Integrity Declaration

The authors confirm that this research complies with accepted standards of research integrity. The study involved no data fabrication, no results falsification, and no p-hacking or selective reporting. The work is original, has not been previously published, and all methods were conducted ethically.

5.9. Originality & Plagiarism Statement

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6. HUMAN AND ANIMAL-RELATED STUDIES

6.1. Ethical Approval

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki for research involving human

participants. Ethical and academic approval was obtained from the Council of the University of Kufa, College of Science, under official letter No. 5373 dated October 1, 2025. In addition, administrative and research approval to conduct the study in healthcare facilities was granted by the Najaf Health Directorate, Ministry of Health, Iraq, through the Training and Human Development Center, under official letter No. 27321 dated October 7, 2025. The approval permitted conducting the study at the Specialized Hospital for Gastrointestinal and Liver Diseases in Al-Najaf Al-Ashraf, Iraq.

All participants were informed of the study's purpose and procedures prior to enrollment, and written informed consent was obtained from each participant. The confidentiality of personal information was strictly maintained, and all collected data and biological samples were used exclusively for scientific research purposes..

6.2. Informed Consent

The participants involved in the current study were patients seeking diagnosis and treatment at the Gastroenterology and Hepatology Specialized Center in Al-Najaf Al-Ashraf, Iraq, for standard diagnostic evaluations. Biological specimens and relevant data were collected following defined laboratory protocols. Verbal informed consent was obtained from all adult participants, whereas consent for minors was collected from a parent or legal guardian. Participants were informed of the study's aims and their right to withdraw from participation at any moment. All gathered data were anonymized and assigned unique identifiers prior to analysis, with access rigorously restricted to the research team to preserve anonymity and comply with ethical standards.

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Table 1. *Demographic, Clinical, and Biochemical Characteristics of GI Patients and Healthy Controls*

Variable	GI patients N=88	Controls N=40	95% CI	p-value
Age (yr.)	36.81 ± 13.88	35.38 ± 10.78	-3.05 – 5.91	0.564
>35	44 (50.0%)	19 (47.5%)		0.602 χ^2= 1.02
25–34	26 (29.5%)	15 (37.5%)		
15–24	18 (20.5%)	6 (15.0%)		
Sex				
Male	26 (29.5%)	18 (45.0%)		χ^2= 2.912 0.088
Female	62 (70.5%)	22 (55.0%)		
BMI	26.25 ± 3.45	24.90 ± 2.95	0.16 – 2.53	0.026*
Obese	13 (14.8%)	5 (12.5%)		0.256 χ^2= 2.73
Overweight	38 (43.2%)	12 (30.0%)		
Normal weight	37 (42.0%)	23 (57.5%)		
Glucose (mg/dL)	106.62 ± 21.43	91.38 ± 9.66	9.80 – 20.67	<0.001*
Hb (g/dL)	11.75 ± 1.57	12.71 ± 1.16	-1.46 – -0.47	<0.001*
Anemia				
Moderate	12 (13.6%)	3 (7.5%)		0.052 χ^2= 5.90
Mild	30 (34.1%)	7 (17.5%)		
Normal	46 (52.3%)	30 (75.0%)		
ALT (U/L)	12.68 ± 6.06	14.91 ± 5.35	-4.34 – -0.11	0.040*
AST (U/L)	16.92 ± 5.20	18.97 ± 5.45	-4.09 – -0.01	0.049*
T.S.B (mg/dL)	0.35 ± 0.10	0.37 ± 0.11	-0.06 – 0.02	0.376
TC (mmol/L)	4.11 ± 0.89	4.20 ± 0.71	-0.39 – 0.20	0.525
LDL (mmol/L)	1.92 ± 0.86	2.17 ± 0.74	-0.54 – 0.05	0.105
TG (mmol/L)	2.13 ± 0.58	1.42 ± 0.37	0.54 – 0.88	<0.001*
HDL (mmol/L)	1.21 ± 0.20	1.37 ± 0.18	-0.23 – -0.09	<0.001*
TG/HDL	1.87 ± 0.76	1.06 ± 0.38	0.61 – 1.01	<0.001*
AIP Class				
Moderate to High (>2)	35 (39.8%)	3 (7.5%)		<0.001* χ^2= 13.72
Normal (<2)	53 (60.2%)	37 (92.5%)		
Nes-1	11.82 ± 2.19	20.20 ± 7.14	-10.71 – -6.06	<0.001*
Medication				
Primary diagnosis	35 (39.8%)	0 (0.0%)		0.037* χ^2= 6.57
Yes	35 (39.8%)	0 (0.0%)		
Biology	18 (20.5%)	0 (0.0%)		

Significant differences at *p<0.05. Continuous variables as Mean ± SD and 95% CI. Categorical variables as N (%), χ^2, and p-value. AIP: Atherogenic index plasma

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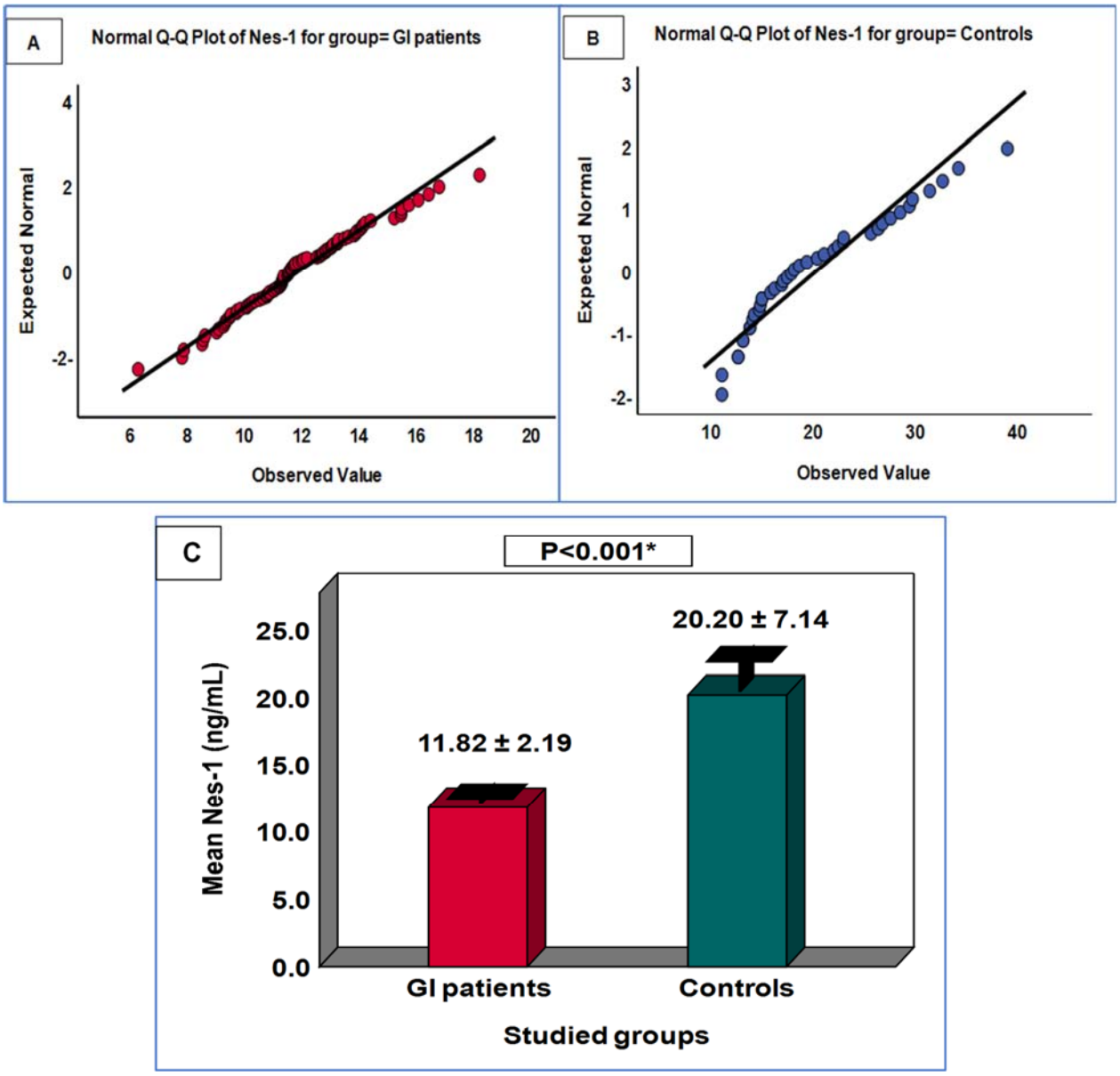

Figure 1. *The Q–Q plots of the Normal Distribution of Nes-1 in the GI and the Control groups*

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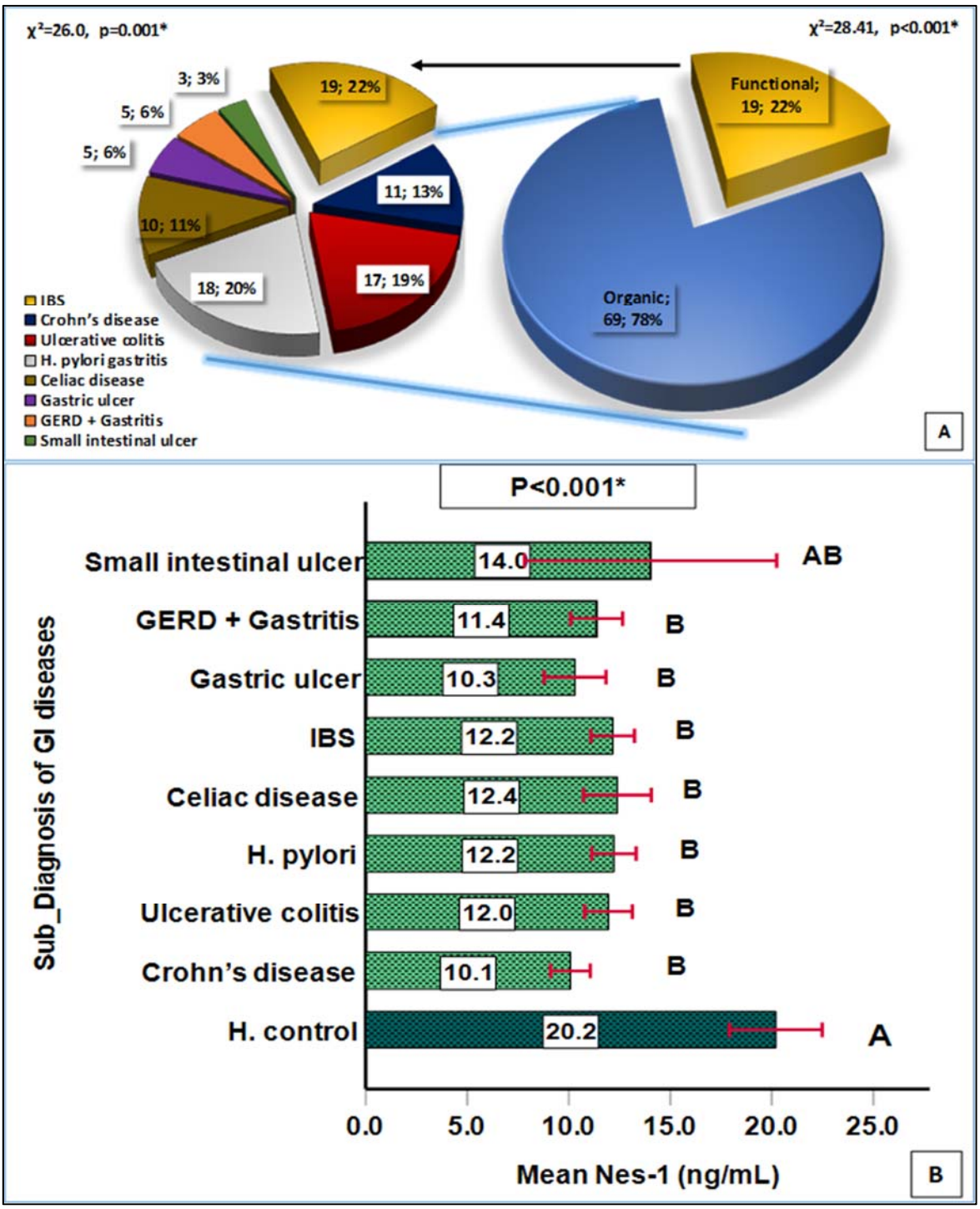

Figure 2. *Distribution of gastrointestinal disease, subdiagnosis, and serum Nesfatin-1 levels among patients and healthy controls*

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Table 2. *Univariate linear regression analysis of clinical and biochemical predictors of serum Nesfatin-1 levels in gastrointestinal disease patients*.

Variable	B	Beta	t	p-value	95% CI
Age (yr.)	0.02	0.15	1.08	0.282	-0.02 – 0.07
BMI	-0.26	-0.41	-2.92	0.005**	-0.44 – -0.08
Glucose (mg/dL)	-0.07	-0.73	-9.84	<0.001***	-0.09 – -0.06
Hb (g/dL)	0.26	0.18	1.74	0.086	-0.04 – 0.55
ALT (U/L)	0.02	0.05	0.44	0.660	-0.06 – 0.09
AST (U/L)	-0.00	-0.00	-0.04	0.972	-0.09 – 0.09
T.S.B (mg/dL)	-2.14	-0.09	-0.87	0.385	-7.01 – 2.73
TC (mmol/L)	-0.90	-0.37	-3.66	<0.001***	-1.39 – -0.41
LDL (mmol/L)	-1.01	-0.40	-4.03	<0.001***	-1.51 – -0.51
TG (mmol/L)	-0.90	-0.24	-2.30	0.024*	-1.69 – -0.12
HDL (mmol/L)	3.04	0.28	2.69	0.009**	0.79 – 5.29
TG/HDL	-0.75	-0.26	-2.53	0.013*	-1.35 – -0.16

Dependent variable: Nes-1 (ng/mL). Significant differences at *p<0.05, **<0.01, ***<0.001

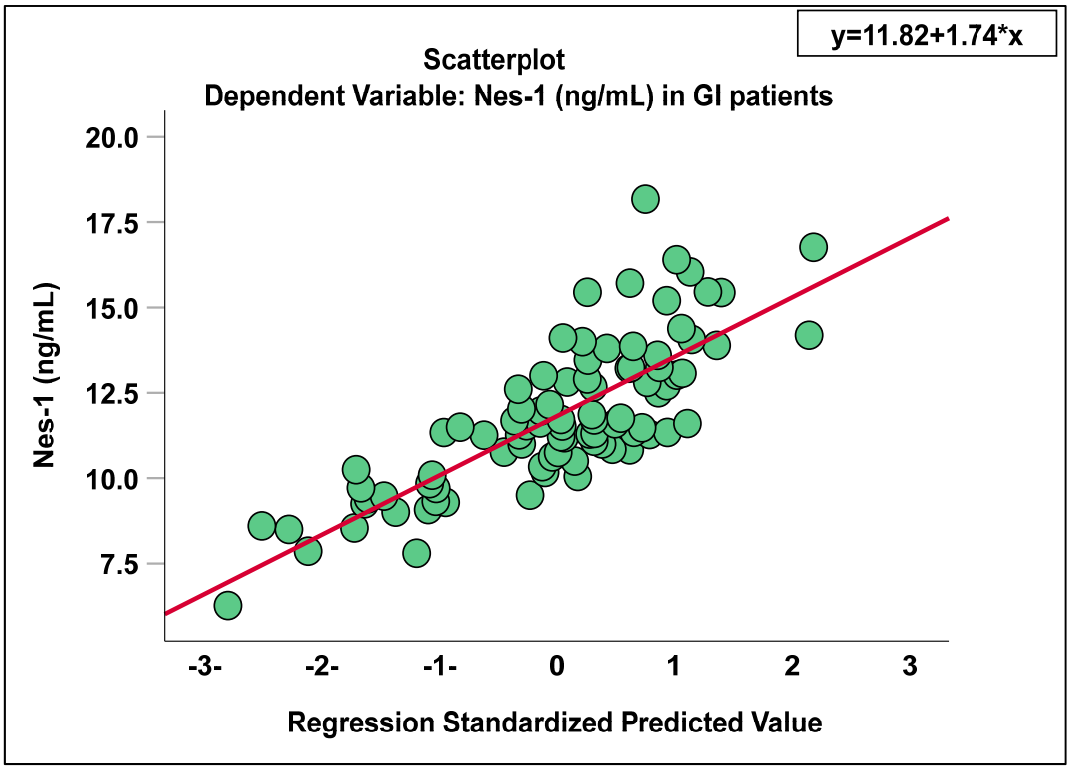

Figure 3. *Linear regression scatterplot of the relationship between standardized predicted values and serum Nesfatin-1 levels in patients with gastrointestinal diseases.*

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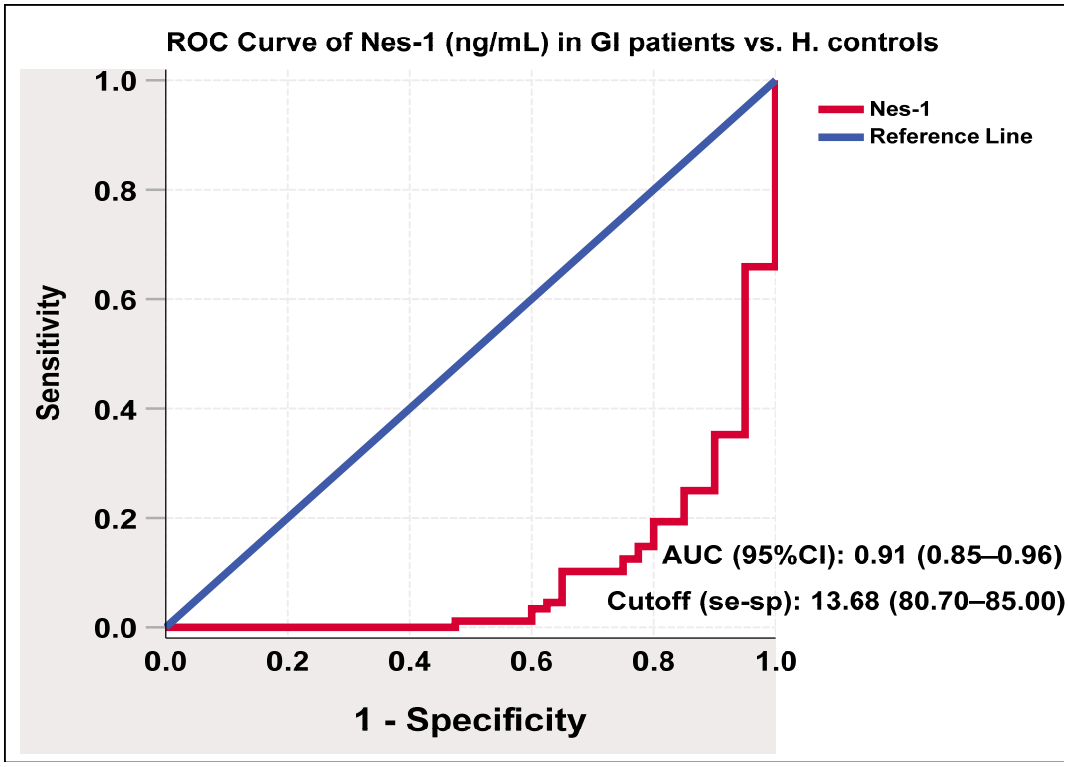

Figure 4. *ROC Curve Analysis of Serum Nesfatin-1 in GI Patients and Healthy Controls*

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