Keywords
Helicobacter pylori; fecal calprotectin; intestinal inflammation; C-reactive protein; white blood cell count; fecal occult blood.

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Association Between Active *Helicobacter pylori* Infection and Fecal Calprotectin Categories: A Cross-Sectional Analytical Study in an Iraqi Clinical Population

Abstract

Background: *Helicobacter pylori* mainly involves the gastric mucosa; however, its connection to fecal calprotectin (FC), an indicator of neutrophilic inflammation in the gastrointestinal tract, is not fully known yet. In the present study, the correlation between *H. pylori* infection and FC categories was determined together with inflammatory, hematologic, nutritional, and stool characteristics of the patients.

Methods:. The present cross-sectional study consisted of 429 subjects aged 4-88 years visiting the Al-Nokhba Private Laboratory, Iraq, due to digestive symptoms or with a clinical suspicion of active infection with *H. pylori* from May 2025 to May 2026. *H. pylori* stool antigen test and ^{13}C-urea breath test were used for active infection with H. pylori. FC values were classified as normal (≤50 µg/g), intermediate (51-250 µg/g), and high (>250 µg/g). CRP, ESR, WBC count, platelets count, hemoglobin, ferritin, zinc, vitamin B12, HbA1c, FOB, red blood cells in stool, and pus cells in stool were investigated. The comparisons of continuous variables were made by the Kruskal–Wallis test, whereas the analysis of categorical variables was performed by Pearson's chi-square test or Fisher's exact test, depending on the nature of the data. Cochran-Armitage trend test was used to evaluate the trend in *H. pylori* positivity among FC groups.

Results: Of the 429 subjects studied, 279 (65.0%) subjects tested positive for *H. pylori* infection. Normal, intermediate and high FC levels were observed in 255 (59.4%), 100 (23.3%), and 74 (17.2%) participants respectively, meaning that 174 subjects (40.6%) had FC levels higher than 50 µg/g. The prevalence of *H. pylori* infection ranged from 48.6% in the normal-FC group to 81.0% in the intermediate FC group and 100% in the high FC group ($p<0.001$; p for trend < 0.001). There were significant differences in CRP levels and WBC count among the FC groups ($p=0.001$ and $p=0.002$, respectively). However, there were no significant differences between the groups in ESR, platelet count, hemoglobin and ferritin level. The same was observed for zinc concentrations ($p = 0.003$). There were no significant differences in vitamin B12 and HbA1c levels. FOB positivity increased from 3.9% in the normal-FC group

Conclusion: FCs in higher categories correlated with increasing *H. pylori* positivity and were also characterized by increased levels of CRP, WBC, and FOB positivity. However, since this result is obtained through an unadjusted cross-sectional analysis, it cannot be concluded that *H. pylori* infection causes increased FC. An elevated level of FC, especially combined with FOB positivity, needs further assessment for other inflammatory and anatomical diseases of the digestive system. In order to elucidate the nature of this correlation, a prospective multicenter study with the use of endoscopic and histological examination and FC testing both before and after treatment is needed.

INTRODUCTION

Helicobacter pylori is an extensively prevalent bacteria that causes persistent infection of the gastric mucosa, causing chronic gastritis. Even though the prevalence of these bacteria has been declining over the last few decades, a systematic review involving 71 countries reported the pooled prevalence of about 43.1% for the period of 2011-2022. The prevalence rate varies significantly depending on geographical location, age, economic factors, and the diagnostic procedure employed. Persistent infection of these bacteria is of clinical significance since it causes dyspepsia, peptic ulcers, MALT lymphoma, and even gastric carcinoma. Clinical guidelines in the current era consider this bacterial infection as an infectious disease that needs diagnosis and treatment [1–3].

The inflammatory reaction to *H. pylori* involves the recruitment of neutrophils, lymphocytes, and other immune cells into the gastric mucosa. The implications of this process may go further than the inflammatory reaction in the stomach. Continuous irritation by the bacteria and the secretion of pro-inflammatory agents may lead to gastrointestinal or systemic inflammation. Such considerations have led to greater interest in non-invasive markers that will provide information on the inflammatory reaction associated with the active infection [4, 5]. The evidence from other chronic infections suggests that bacterial adherence; virulence factors, biofilm production, and antibiotic resistance may aid long-term colonization and sustain the inflammatory response of the host. These mechanisms are different for each bacterial organism and depending on the site of infection but they allow us to gain more insight into inflammatory changes caused by bacteria [6, 7].

Fecal Calprotectin (FC) is a calcium- and zinc-binding protein that is secreted mainly by activated neutrophils. The level of FC in the feces is indicative of the movement and activation of the neutrophils in the gut. FC is a well-established non-invasive marker of intestinal inflammation and is used for the differentiation of inflammatory diseases of the gut from functional diseases and the evaluation of inflammatory activity. Nevertheless, FC is not exclusively a marker of inflammatory bowel disease. Increased levels of FC can be seen in infectious diseases of the gut, drug-induced mucosal injury, malignancy, gastrointestinal bleeding, and other inflammatory processes [8].

Recent research indicates that there is an increased association between FC levels and the infection by *H. pylori* bacteria. In a paediatric study, children who had been diagnosed with *H. pylori* infection through biopsy showed significantly elevated FC levels in comparison with children without the infection. Moreover, the level of FC was positively associated with the intensity of inflammation of neutrophils in the stomach [9]. Another recent study on pediatric subjects demonstrated similar results regarding higher FC and increases in serum markers of systemic inflammation in patients with *H. pylori* infection [10]. In adult population, a prospective study indicated higher FC levels in infected patients in correlation with the degree of gastric inflammation induced by *H. pylori*, with decrease in FC concentration after successful eradication therapy [11].

The interaction between the infection of *H. pylori* and the systemic inflammation has also been unclear. It has been shown by some population-based studies to be associated with higher prevalence of high level of CRP, indicating a possible low-grade systemic inflammatory reaction. However, one big study of asymptomatic adults indicated there is no correlation between infection and C-reactive protein and other markers of systemic inflammation independent of the adjusted confounding factors [12,13]. Such inconclusive findings suggest that the measurement of FC needs to be considered along with the markers of systemic inflammation and hematology such as CRP, erythrocyte sedimentation rate, white blood cell count, platelet count, hemoglobin, and ferritin.

The previous studies usually targeted selected pediatric or adult population and analyzed FC concentration or gastric histology findings separately. There are few studies which have looked at all such criteria together, including predefined category of FC, active infection of *H. pylori*, markers of systemic inflammation, hematology parameters, nutritional and glycemic parameters, and stool findings. There are also very few studies based on Iraqi clinical populations.

Hence, the main aim of this study was to evaluate the relationship between the presence of an active *H. pylori* infection and the predetermined FC categories and see if there was any progressive increase in *H. pylori* positivity according to these categories amongst subjects whose age range was wide. The second aim of the study was to identify the profile of laboratory results associated with these conditions through comparison of inflammatory, hematological, nutritional, glycemic, and stool parameters amongst the various FC categories.

1. MATERIALS AND METHODS

Study Design and Setting

A cross-sectional analytic study was carried out in Al-Nokhba Private Laboratory, Iraq, from May 2025 to May 2026. Participants included people above 4 years of age who visited the laboratory with symptoms of the gastrointestinal tract or had been referred to the laboratory for suspected active *H. pylori* infection.

All participants met predetermined inclusion criteria, and each individual underwent procedures as mentioned in the research protocol.

Participant Recruitment

Subjects were enrolled through the process of consecutive sampling without probability sampling. Participants were consecutively screened for the inclusion criteria until the required number of participants was reached.

The clinical impression of an *H. pylori* infection was based on the presence of one or more gastrointestinal symptoms, such as dyspepsia, epigastric pain or discomfort, nausea, abdominal bloating, changes in bowel habits, or other gastrointestinal symptomatology.

Inclusion and Exclusion Criteria

The subjects had to meet the following inclusion criteria: age of 4 years or older; presence of gastrointestinal symptoms; suspicion of an active *H. pylori* infection. They had to have the adequate amount of samples (feces and venous blood) and perform the following tests: *H.*

pylori diagnosis tests and fecal calprotectin determination. Also, there was enough clinical and laboratory information to conduct the main analysis.

Participants were excluded if they had received antibiotics or bismuth-containing medications during the four weeks preceding *H. pylori* testing or proton-pump inhibitors during the preceding two weeks, because these medications may reduce the sensitivity of diagnostic testing.

Additional exclusion criteria included a previously confirmed diagnosis of inflammatory bowel disease, gastrointestinal malignancy, or celiac disease; recent gastrointestinal surgery; acute infectious diarrhea; confirmed intestinal parasitic infection; or overt gastrointestinal bleeding at recruitment. Inadequate volume, contamination, improper collection, labeling, leakage, and unsuitable storage of samples were all grounds for their exclusion. Subjects whose main *H. pylori* diagnostic results were incomplete or lacked the fecal calprotectin measurement were also excluded from the main analysis.

Sample-Size Estimation

The minimum required sample size was estimated using Cochran's formula for cross-sectional studies:

$$n = Z^2p(1 - p) / d^2 \quad [14]$$

Where n is the minimum sample size that would be required, Z is the standard normal value of a 95% confidence level (Z = 1.96), p is the estimated proportion of the characteristic being investigated, and d is the margin of error that can be accepted.

Since an adequately precise estimate was not available for the target clinical population, the value for p was taken to be 0.50, yielding the most conservative sample-size estimate, while the value of d was taken to be 0.05. The resulting minimum sample size worked out to be about 384. In order to compensate for any incomplete data or unsuitable samples, the minimum sample size was inflated by 10% to yield a target sample size of about 423 individuals. Thus, the actual study population consisted of 429 individuals and hence exceeded the minimum sample size requirement.

Ethical Considerations

The study protocol was submitted for review and approval by the appropriate institutional ethical board. Informed verbal consent was sought from each adult participant prior to participation and specimen collection. In case of participants below the age of 18, verbal consent was sought from their parent or guardian. Verbal consent was obtained in accordance with the stipulations of the ethical committee granting the approval. Privacy and confidentiality of the participants was ensured through the research process. All the participants and specimens were identified by unique coded numbers in the laboratory records, and there was no unrestricted access to personally identifying information.

Specimen Collection and Processing

The fresh fecal specimens and venous blood samples were obtained from the study subjects in the laboratory settings following standard procedures. All the specimens were then labeled using codes associated with the study subject ID numbers

Stool Specimen Collection and Processing

Fecal samples were collected in sterile, dry, leak-proof, and properly labeled plastic containers. Individuals, or their parents/legal guardians in the case of minors, were advised to ensure that the samples were not contaminated with urine, water, toilet paper, and disinfectants.

Samples were delivered to the laboratory immediately. Those designated for conventional microscopic evaluation were analyzed within 20-30 minutes after collection. A portion of each sample was set aside for direct microscopic evaluation, fecal occult blood test, Helicobacter pylori stool antigen test, and fecal calprotectin test. Each portion was then analyzed according to the needs of the respective test.

The test for direct microscopic evaluation was designed to detect red blood cells, pus cells, and parasites. Fecal calprotectin was measured after processing of the assigned portion following the extraction protocol recommended by the test manufacturer. If immediate analysis was not feasible, the unprocessed fecal samples were kept in the refrigerator (2-8°C) for no more than 72 hours. Those extract aliquots which required storage for longer periods were stored at −20°C until analyzed. Multiple freeze-thaw cycles were to be avoided.

Blood Sample Collection and Processing

Venous blood samples were collected from each individual by venipuncture and distributed into proper collection tubes based on the needs of the intended laboratory analyses.

Blood collected in EDTA tubes was used for determining the complete blood count and glycated hemoglobin levels. The determination of serum levels of zinc, vitamin B12, ferritin, and C-reactive protein were performed using serum separator gel tubes. Erythrocyte sedimentation rate was determined using sodium citrate tubes, where the ratio of blood to sodium citrate is 4:1.

EDTA and sodium citrate tubes were gently inverted immediately after sampling to ensure proper mixing with the anticoagulant agent to prevent clotting. Complete blood count, glycated hemoglobin, and erythrocyte sedimentation rate determinations were done within the specified stability period of each method of analysis. Serum separator tubes were left to clot at room temperature for 30 minutes, after which they were centrifuged at 1,500 × g for 10 minutes. The obtained serum was collected in coded tubes and assayed as soon as possible. If not, serum specimens were kept at 2–8°C, but no longer than 48 hours before analysis. Specimens that needed further storage time were made into aliquots and stored at −20°C prior to testing. Multiple freeze and thaw cycles were avoided. Specimens having insufficient quantity, inappropriate labelling, leakage, contamination, hemolysis, or clot formation in anticoagulated tubes were rejected and reassumed.

Determination of *Helicobacter pylori* Status

Active *Helicobacter pylori* infection was assessed using the *H. pylori* stool antigen test and the ^{13}C-urea breath test.

***H. pylori* Stool Antigen Test**

For the detection of *H. pylori* antigen in fresh stool samples, the OnSite® *H. pylori* Ag Rapid Test CE (Cat. No. R0192C; CTK Biotech, Poway, California, USA) was used. It is an immunochromatographic qualitative test that detects *H. pylori* antigen in human fecal specimens. Each stool sample was placed in the provided extraction device

with the buffer and mixed thoroughly to create the homogenous suspension. The created suspension was then added to the sample well of the test cassette, and the result was read after 10 minutes according to the manufacturer's guidelines.

The presence of the control line indicated that the test was performed correctly. If the control line and the test line were both present, the result was considered positive; otherwise, it was negative. The absence of the control line made the test invalid, and it had to be repeated with another test cassette.

^{13}C-Urea Breath Test

The ^{13}C-urea breath test was carried out using the Heliforce® Urea [^{13}C] Breath Test Kit, which included 50 mg of ^{13}C-urea (Beijing Richen-Force Science & Technology Co., Ltd., Beijing, China). The breath samples were tested using the Richen IR-force 200 ^{13}C-urea breath test analyzer provided by the same company.

Fasting for at least four hours prior to the testing and two weeks of stopping the proton-pump inhibitors were mandatory. Meanwhile, discontinuing the antibiotic and bismuth medications was necessary for at least four weeks before the test.

A baseline breath sample was obtained prior to the delivery of the labeled urea. After that, patients received 50 mg of ^{13}C-urea (as recommended by the manufacturer). A breath sample was taken 30 minutes after the administration. Both breath samples were measured with the IR-force 200 analyzer. The outcome was calculated as the difference in the $^{13}CO_2/^{12}CO_2$ ratio before and after the dose and expressed as the difference over baseline (DOB). A DOB of ≥4.0‰ was considered positive for active H. pylori infection, while a DOB of <4.0‰ was considered negative. *H. pylori* was determined to be positive if the fecal antigen test and ^{13}C-urea breath test were both positive, while *H. pylori* was negative if both tests were negative. In case of discrepant results, both tests would be repeated. The final *H. pylori* status was based on consistent repeated testing results.

Hematological Measurements

Total white blood cell count, hemoglobin concentration, and platelet count were estimated from EDTA-anticoagulated whole blood by means of a fully automatic hematology analyzer (Beckman Coulter DxH 500, USA) in accordance with the manufacturer's protocol.

Counts of white blood cells and platelets were assessed by impedance method while concentration of hemoglobin was assessed by photometry. The values for white blood cell and platelet counts were presented as $\times 10^9$/L while that for hemoglobin concentration as g/dL.

Erythrocyte Sedimentation Rate

The measurement of erythrocyte sedimentation rate in blood samples anticoagulated with sodium citrate was done by the use of the MICROsed-System® (ELITechGroup/Vital Diagnostics, France/USA) based on the Westergren modification. The results are

Glycated Hemoglobin Measurement

The measurement of glycated hemoglobin was done from EDTA-anticoagulated whole blood in the cobas® c 111 Clinical Chemistry Analyzer (Roche Diagnostics GmbH, Germany). The test was done using the Tina-quant® Hemoglobin A1c Gen.3 (A1C-3) assay (Roche Diagnostics) as per manufacturer's guidelines.

Measurement of Serum Biomarkers

The serum levels of vitamin B12 and ferritin were analyzed using the cobas® pro integrated system with the cobas e immunoassay analytical system (Roche Diagnostics, Germany).

Vitamin B12 levels were detected by Elecsys® Vitamin B12 II test while the ferritin levels were detected by Elecsys® Ferritin test. Both determinations were performed according to electrochemiluminescence immunoassay technique.

Serum C-reactive protein levels were estimated using the cobas® c 111 clinical chemistry analyzer and Cardiac C-Reactive Protein (Latex) High Sensitive test (CRPHS; Roche Diagnostics, Germany). The estimation was done according to immunoturbidimetric method, and the values were presented in mg/L.

Serum zinc level was determined using the Randox Zinc assay with deproteinisation kit (Cat. No. ZN2341; Randox Laboratories Ltd., Crumlin, United Kingdom) on the RX Daytona+ clinical chemistry analyzer from the same company. The method was based on colorimetry, and values were reported in µg/dL.

The testing in the laboratory was carried out according to the manufacturers' recommendations and laboratory standard operating procedures. Calibration and quality control of the equipment were conducted according to the requirements set forth by the particular manufacturers. Results were reported provided that quality control criteria were fulfilled.

Routine Stool Examination

Stool test was done within 20–30 min after specimen collection. About 2 mg of fresh stool was suspended in 0.9% saline solution on a sterile glass slide for the preparation of a wet mount. The slides were first observed using ×10 magnification and then using ×40 magnification for the determination of the presence of red blood cells, pus cells, and parasites.

Red blood cell and pus cell counts were reported in terms of 0–2, 3–5, 6–10, or >10 cells/HPF. For statistical analyses, 0–2 cells/HPF were considered negative results while ≥3 cells/HPF were considered positive results. Individuals with the presence of intestinal parasitic structures were excluded according to the inclusion/exclusion criteria.

Fecal Occult Blood Testing

Occult fecal blood was detected by using OnSite® FOB Rapid Test CE (Cat. No. R2010C; CTK Biotech, Poway, CA, USA). It is an immunoassay test that can detect human hemoglobin in fecal samples qualitatively.

One part of the stool sample was placed into the sample container filled with 2 mL of extraction buffer as recommended by the manufacturer. Prepared extract was then added to the sample window of the test cassette, and the result was read at the 10-minute mark. All results read at any other time were considered invalid.

When two bands appeared on the test strip (control and test), the result was considered positive. When only one band (control) was present, the result was considered negative. If there was no control band visible at all, the test was invalid and needed to be repeated using another test cassette. The lowest level of human hemoglobin detectable in this assay was 50 ng/mL.

Fecal Calprotectin Quantification

The fecal calprotectin level was determined by employing the Alegria® automated ELISA system and Alegria® Calprotectin test strips (Catalog Number: ORG 280; ORGENTEC Diagnostika GmbH, Mainz, Germany).

Fresh stool samples were extracted following the manufacturer's protocols, which included use of stool extraction tubes and extraction buffer provided by the manufacturer. Stool samples were well homogenized in the extraction media and supernatant was generated following manufacturer's procedure. The supernatant was further used for loading on the Alegria® automated system.

Incubation, wash steps, conjugate reaction, substrate development, calibration, and quantitation of fecal calprotectin were done automatically by Alegria®. Fecal calprotectin levels were measured in microgram per gram of stool (µg/g).

Calibration of the instrument and internal quality control were conducted as directed by the manufacturer and by the laboratory's protocol. Only those results that met the internal quality control criteria were considered valid.

In the statistical analysis, three categories of fecal calprotectin level were set, namely normal level (≤50 µg/g), elevated at medium level (51-250 µg/g), and high elevation level (>250 µg/g).

Statistical Analysis

Statistics was done using software R (version 4.4.2). Continuous variables such as age and laboratory biomarkers were described by median with interquartile range, whereas categorical variables were described by frequency and percentage. Continuous variables such as age and laboratory biomarkers were compared among the three categories of fecal calprotectin using Kruskal-Wallis test. Fecal calprotectin levels were described descriptively according to each category and not statistically analyzed since the three categories were defined on the basis of fecal calprotectin. Categorical variables were compared among the three categories of fecal calprotectin using Pearson's chi-square test. All tests were bilateral, and any p value of <0.05 was taken as significant.

2. RESULTS

Sociodemographic and Clinical Characteristics of the Study Population

Subjects for the experiment included 429 subjects having an average age of 37 years with an interquartile range of 27-51 years. The highest proportions of the subjects were in the age group of 19-40 years (48.7%) followed by those in the age group of 41-60 years (29.8%). The age group of 61-88 years had 13.1% subjects whereas the age group of 4-18 years had 8.4% subjects. The proportion of males was 57.1%, and that of females was 42.9%. Regarding *H. pylori* status, out of 429 subjects, 279 subjects had *H. pylori* positive result (65.0%), while 150 subjects had negative result (35.0%). This indicates that two-thirds of the subjects participating in the study had *H. pylori* infection, as presented in Table 1.

Table 1. Sociodemographic and Clinical Characteristics of the Study Population (n = 429)

Characteristic	Total study population
Age, median (IQR), years	37 (27–51)
Age group, n (%)	
4–18 years	36 (8.4)
19–40 years	209 (48.7)
41–60 years	128 (29.8)
61–88 years	56 (13.1)
Sex, n (%)	
Female	184 (42.9)
Male	245 (57.1)
H. pylori status, n (%)	
Negative	150 (35.0)
Positive	279 (65.0)

Distribution and Characteristics of Participants Across Fecal Calprotectin Categories

It is evident from Figure 1 that 255 participants (59.4%) had fecal calprotectin concentration within the normal range (≤50 µg/g), while 100 (23.3%) had intermediate elevation (51–250 µg/g) and 74 (17.2%) had high elevation (≥250 µg/g) levels. A total of 174 participants (40.6%) had fecal calprotectin concentration greater than the normal range.

The median value of fecal calprotectin was 12 µg/g (IQR: 4–26.45) in the normal range group, 103 µg/g (IQR: 71–165) in the intermediate elevation group, and 662.

As shown in Table 2, there was no significant difference in median age among the three fecal calprotectin groups (p = 0.982). There was no significant difference in age group distribution (p = 0.829) and gender distribution (p = 0.623). On the other hand, *H. pylori* status showed a significant difference among fecal calprotectin groups (p < 0.001). The prevalence of *H. pylori*-positive individuals was 48.6% in the normal group, 81.0% in the intermediate elevation group, and 100% in the high elevation group. The Cochran-Armitage trend test revealed that there was a significant trend of *H. pylori* positivity among ordered fecal calprotectin groups (p for trend < 0.001). This suggests that there is a significant relationship between *H. pylori* positivity and fecal calprotectin category while there is no significant relationship between age/sex and fecal calprotectin category.

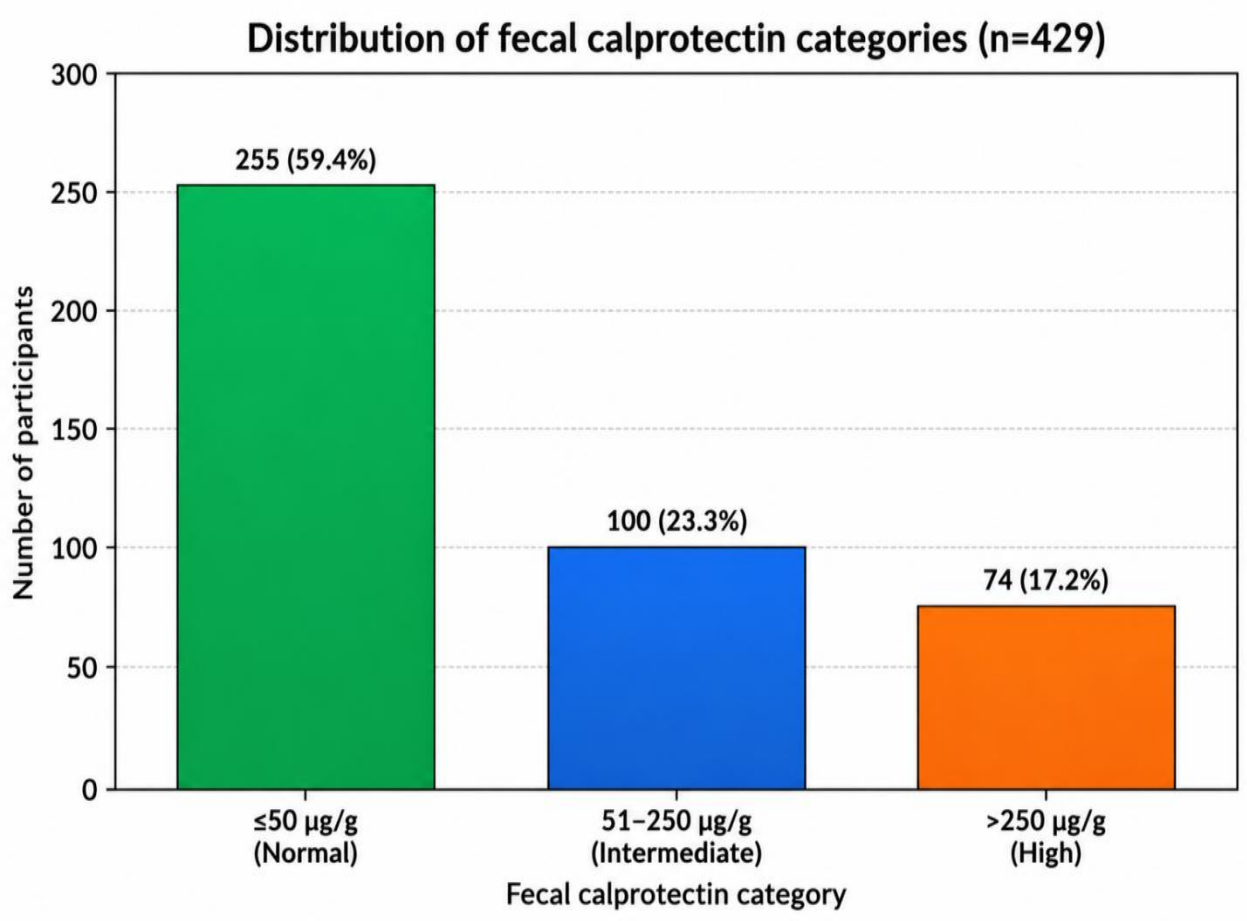

Figure 1. Distribution of participants across fecal calprotectin categories

Table 2. Demographic and clinical characteristics according to fecal calprotectin category

Characteristic	Total (n = 429)	≤50 µg/g, normal (n = 255)	51–250 µg/g, intermediate elevation (n = 100)	>250 µg/g, high elevation (n = 74)	p-value
Fecal calprotectin, median (IQR), µg/g	—	12 (4–26.45)	103 (71–165)	662.5 (469–796.25)	—
Age, median (IQR), years	37 (27–51)	37 (27–50)	38 (27–51)	35 (26–52)	0.982
Age group, n (%)					
4–18 years	36 (8.4)	20 (7.8)	9 (9.0)	7 (9.5)	0.829
19–40 years	209 (48.7)	129 (50.6)	45 (45.0)	35 (47.3)	
41–60 years	128 (29.8)	73 (28.6)	35 (35.0)	20 (27.0)	
61–88 years	56 (13.1)	33 (12.9)	11 (11.0)	12 (16.2)	
Sex, n (%)					0.623
Female	184 (42.9)	107 (42.0)	47 (47.0)	30 (40.5)	
Male	245 (57.1)	148 (58.0)	53 (53.0)	44 (59.5)	
H. pylori status, n (%)					<0.001
Negative	150 (35.0)	131 (51.4)	19 (19.0)	0 (0.0)	
Positive	279 (65.0)	124 (48.6)	81 (81.0)	74 (100.0)	

Data are presented as median (IQR) or number (percentage). The Kruskal–Wallis test was used to compare age, while the chi-square or Fisher's exact test was used for categorical variables, as appropriate. The Cochran–Armitage test was used to assess the trend in *H. pylori* positivity across ordered fecal calprotectin categories. A p-value < 0.05 was considered statistically significant.

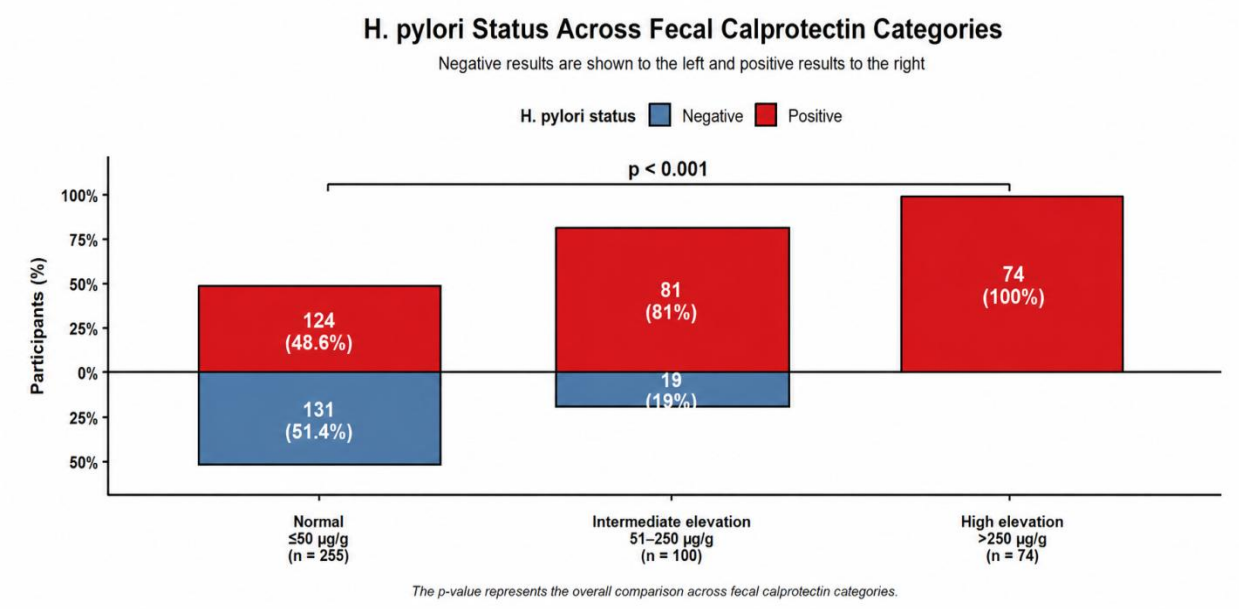

Figure 2. Distribution of *Helicobacter pylori* Status Across Fecal Calprotectin Categories

Figure 2 demonstrates the step-wise rise in the positivity of *H. pylori* based on the fecal calprotectin category. Of the individuals in the normal category of fecal calprotectin levels, 124 out of 255 (48.6%) were positive for *H. pylori*. In the intermediate elevation category, this rate increased to 81 out of 100 individuals (81.0%). In the high elevation category, all 74 individuals were positive for *H. pylori* infection. Consequently, the percentage of negative participants for *H. pylori* was reduced from 51.4% in the normal category to 19.0% in the intermediate category and 0.0% in the high elevation category.

Inflammatory and Hematological Markers Across Fecal Calprotectin Categories

The median CRP levels were higher for all fecal calprotectin categories, increasing from 1.00 mg/L (IQR: 0.72–3.00) in the normal category, to 2.25 mg/L (IQR: 1.00–4.67) in the intermediate elevation category, and finally to 3.25 mg/L (IQR: 2.00–7.15) in the high elevation category. Overall, the differences between the three categories were statistically significant (p = 0.001) as shown in Figure 3 below and in Table 3.

The same trend of increased counts was observed in the median WBC level. There was an increase from 6.95 x 10^9/L (IQR: 5.89–7.92) in the normal category, to 7.69 × 10^9/L (IQR: 6.26–8.99) in

The median ESR and platelet counts were greater in the medium and high-altitude groups compared to the normal group, though these differences were not statistically significant (p = 0.102 and p = 0.056, respectively). The median concentration of hemoglobin was not significantly different between the three groups (p = 0.848). Ferritin concentrations, which are provided in Table 3 but not depicted in Figure 3, were also found to be statistically insignificant when comparing the three groups (p = 0.639).

In summary, there were statistically significant differences among fecal calprotectin categories with respect to CRP and WBC count, while ESR, platelets, hemoglobin, and ferritin were not significantly different.

Table 3. Inflammatory and Hematological Markers According to Fecal Calprotectin Categories

Inflammatory and hematological marker	Total (n = 429)	≤50 µg/g, normal (n = 255)	51–250 µg/g, intermediate elevation (n = 100)	>250 µg/g, high elevation (n = 74)	p-value
CRP (mg/L), median (IQR)	1.30 (0.88–4.00)	1.00 (0.72–3.00)	2.25 (1.00–4.67)	3.25 (2.00–7.15)	0.001
ESR (mm/h), median (IQR)	8.00 (3.00–14.00)	7.00 (3.00–14.00)	8.00 (5.00–14.25)	9.00 (8.00–21.75)	0.102
WBC count (×10^9/L), median (IQR)	7.00 (6.00–8.20)	6.95 (5.89–7.92)	7.69 (6.26–8.99)	8.02 (6.96–9.93)	0.002
Platelet count (×10^9/L), median (IQR)	239.00 (198.00–286.50)	237.50 (195.50–276.25)	262.00 (212.00–314.00)	271.00 (203.25–316.75)	0.056
Hemoglobin (Hb, g/dL), median (IQR)	14.60 (13.10–15.88)	14.60 (13.25–15.90)	14.20 (12.90–15.80)	14.85 (13.03–15.65)	0.848
Ferritin (ng/mL), median (IQR)	70.95 (38.00–164.00)	64.50 (38.00–163.00)	76.90 (38.25–145.75)	75.95 (62.50–244.75)	0.639

Data are presented as median (interquartile range, IQR). Comparisons among the fecal calprotectin categories were performed using the Kruskal–Wallis test. A p-value < 0.05 was considered statistically significant.

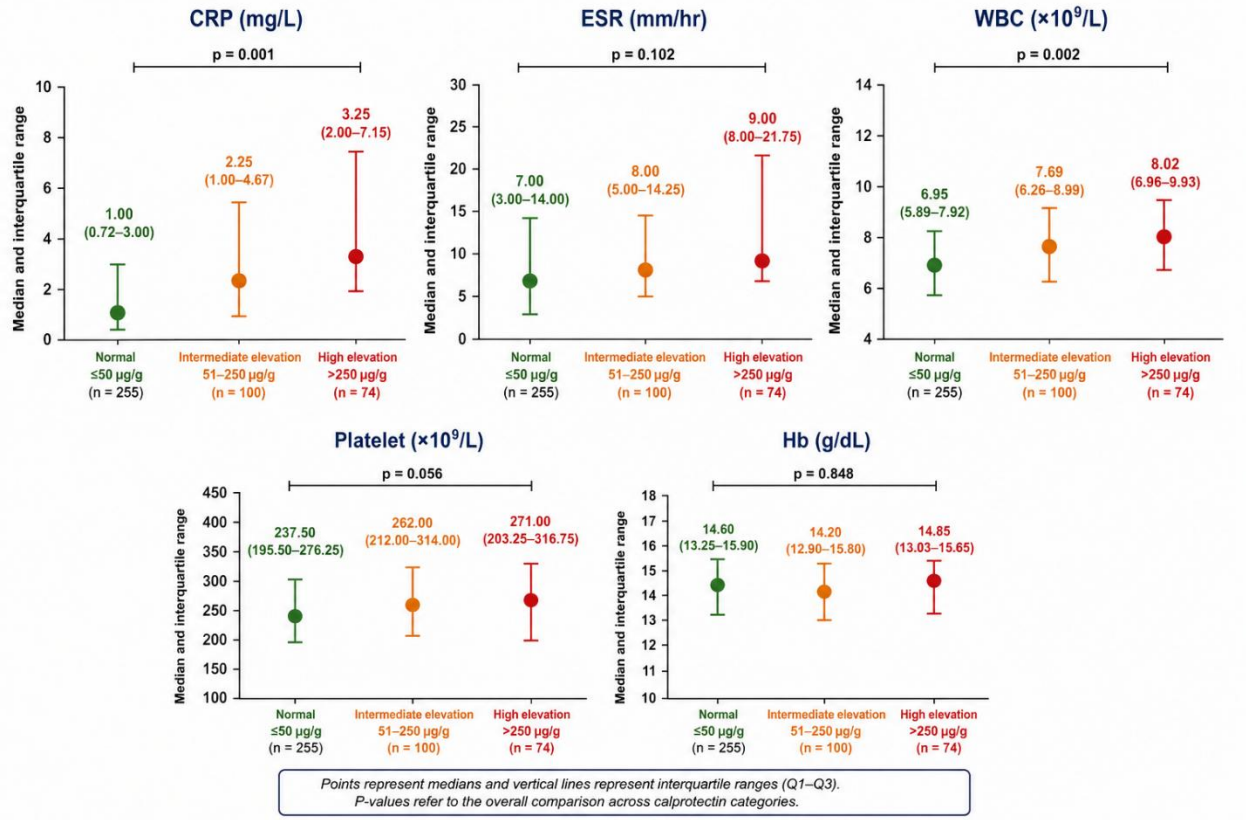

Figure 3. Median and Interquartile Range of Selected Inflammatory and Hematological Markers Across Fecal Calprotectin Categories. Points represent medians, and vertical lines represent interquartile ranges. Reported p-values were obtained from the overall Kruskal–Wallis comparison across the three groups.

Nutritional and Glycemic Markers Across Fecal Calprotectin Categories

The median zinc concentration showed statistically significant differences between fecal calprotectin categories, as demonstrated in Table 4 and Figure 4. For the normal category, the median zinc concentration was 86.00 µg/dL (IQR: 81.00–90.00) while for the intermediate-elevation category, the median was 93.50 µg/dL (IQR: 87.00–98.75) and for the high-elevation category, the median was 85.00 µg/dL (IQR: 79.00–87.00). The difference between all the three categories was statistically significant (p = 0.003). The medians had a non-monotonic trend where the median zinc concentration was highest in the intermediate elevation category.

Median concentrations of vitamin B12 were greater in the intermediate- and high-elevation groups compared to the normal category but there was no statistically significant difference (p = 0.616). Also, there was no significant difference between the three fecal calprotectin categories in median HbA1c concentration (p = 0.973). Of all the markers studied, zinc was the only one with a statistically significant difference between the three fecal calprotectin categories.

Table 4. Nutritional and Glycemic Markers According to Fecal Calprotectin Categories

Nutritional or glycemic marker	Total (n = 429)	≤50 µg/g, normal (n = 255)	51–250 µg/g, intermediate elevation (n = 100)	>250 µg/g, high elevation (n = 74)	p-value
Zinc (µg/dL), median (IQR)	86.50 (81.78–91.00)	86.00 (81.00–90.00)	93.50 (87.00–98.75)	85.00 (79.00–87.00)	0.003
Vitamin B12 (pg/mL), median (IQR)	425.00 (348.50–627.75)	425.00 (352.50–567.50)	475.00 (333.50–669.75)	494.00 (398.75–590.75)	0.616
HbA1c (%), median (IQR)	5.30 (5.00–5.61)	5.30 (5.00–5.60)	5.35 (5.00–5.60)	5.10 (4.97–5.85)	0.973

Data are presented as median (interquartile range, IQR). Comparisons among the three fecal calprotectin categories were performed using the Kruskal–Wallis test. A p-value < 0.05 was considered statistically significant.

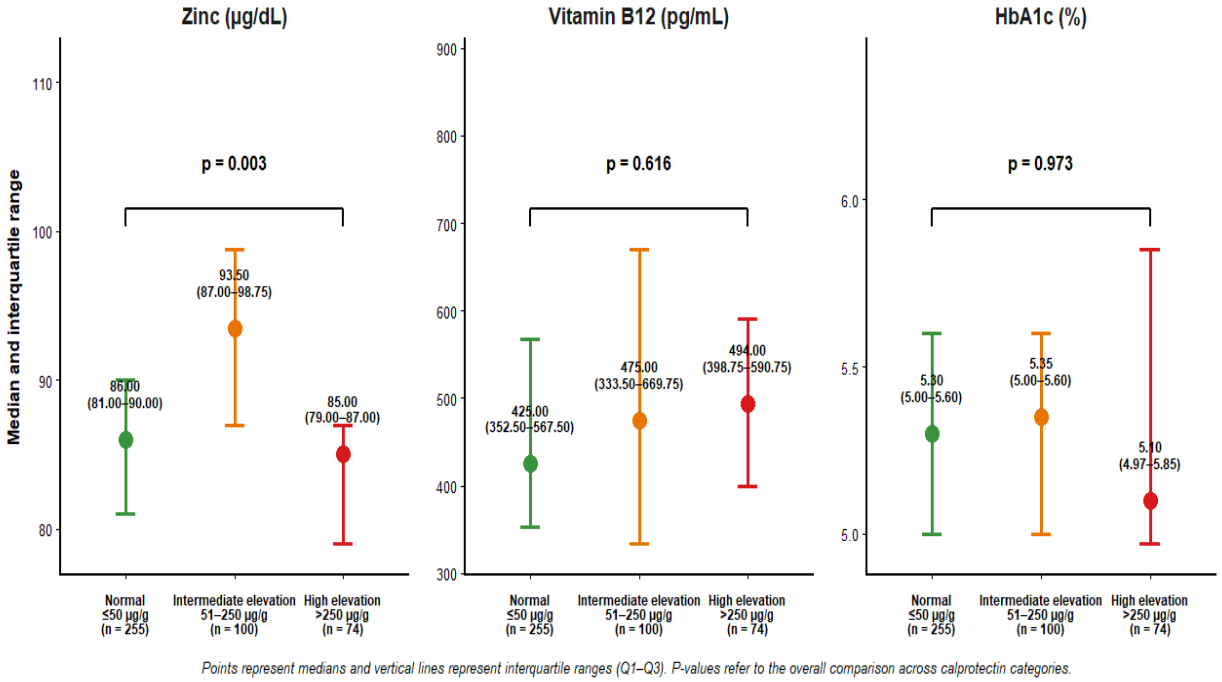

Figure 4. Median and Interquartile Range of Selected Nutritional and Glycemic Markers Across Fecal Calprotectin Categories. Points represent medians, and vertical lines represent interquartile ranges. Reported p-values were obtained from the overall Kruskal–Wallis comparison across the three groups.

Stool Examination Findings Across Fecal Calprotectin Categories

The percentage of positivity for fecal occult blood increased with increasing fecal calprotectin levels as illustrated in Table 5 and Figure 5 below. Positive FOB values were recorded for 10 individuals (3.9%) in the normal category, 8 individuals (8.0%) in the intermediate-elevation category, and 15 individuals (20.3%) in the high-elevation category. The overall association of FOB status with fecal calprotectin category was statistically significant ($p < 0.001$).

In 136 individuals with available results for stool RBCs, the percentages who were positive were 88.7% in the normal category, 81.4% in the intermediate-elevation category, and 81.8% in the high-elevation category. There was no statistically significant difference between the three groups ($p = 0.496$). In the 64 individuals with available results for stool pus-cells, the percentages with positive results were 86.2%, 87.5%, and 84.2%, respectively, and there was no statistically significant difference between the three groups ($p = 0.960$).

Of all the stool examination parameters considered, FOB was the only one which had a significant relationship with fecal calprotectin category. Nevertheless, stool RBC and pus cell counts should be interpreted with caution since these tests were performed on a subset of the studied population.

Table 5. Stool Examination Findings According to Fecal Calprotectin Categories

Stool examination parameter	Total	≤50 µg/g, normal	51–250 µg/g, intermediate elevation	>250 µg/g, high elevation	p-value
Fecal occult blood, n (%)	n = 429	n = 255	n = 100	n = 74	<0.001
Negative	396 (92.3)	245 (96.1)	92 (92.0)	59 (79.7)	
Positive	33 (7.7)	10 (3.9)	8 (8.0)	15 (20.3)	
Stool RBC, n (%)	available n = 136	available n = 71	available n = 43	available n = 22	0.496
Negative	20 (14.7)	8 (11.3)	8 (18.6)	4 (18.2)	
Positive	116 (85.3)	63 (88.7)	35 (81.4)	18 (81.8)	
Stool pus cells, n (%)	available n = 64	available n = 29	available n = 16	available n = 19	0.960
Negative	9 (14.1)	4 (13.8)	2 (12.5)	3 (15.8)	
Positive	55 (85.9)	25 (86.2)	14 (87.5)	16 (84.2)	

Data are presented as number (percentage). Percentages were calculated using the number of participants with available results for each stool examination parameter. The association between FOB status and fecal calprotectin category was assessed using Pearson's chi-square test. Fisher's exact test was used for stool RBC and pus-cell findings because of small expected cell counts. A p-value < 0.05 was considered statistically significant.

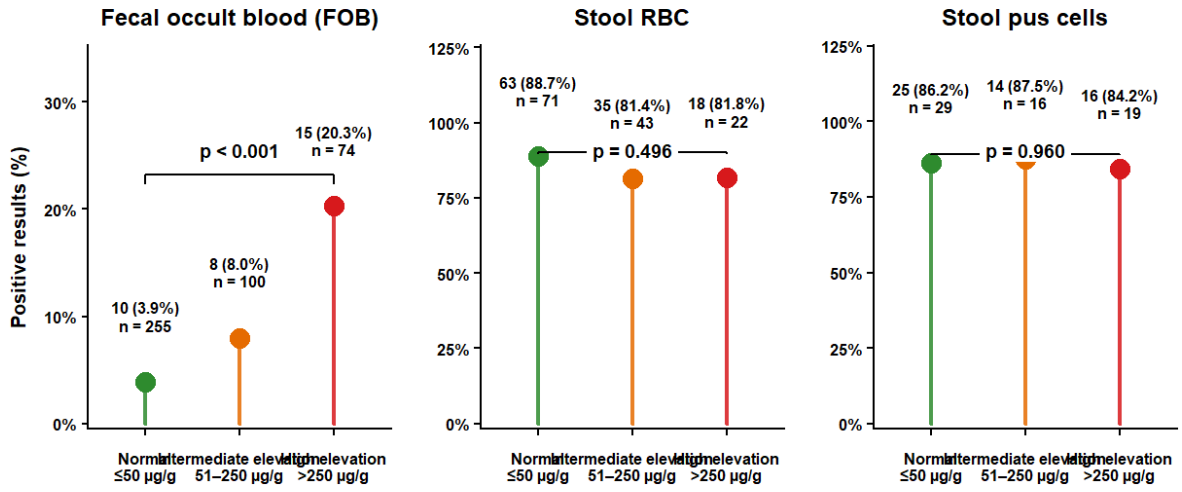

Figure 5. Positive Stool Examination Findings across Fecal Calprotectin Categories. Points represent the percentages of positive results, while labels indicate the number of positive results, percentage, and available sample size. Reported p-values represent the overall comparison across the three categories.

3. DISCUSSION

The present study demonstrated a strong graded association between fecal calprotectin concentration and *Helicobacter pylori* infection. Although 59.4% of the participants had fecal calprotectin concentrations within the normal range, 40.6% had concentrations above 50 µg/g, including 17.2% with concentrations exceeding 250 µg/g. The proportion of *H. pylori*-positive participants increased progressively from 48.6% in the normal fecal calprotectin group to 81.0% in the intermediate-elevation group and 100% in the high-elevation group. All 74 participants in the high-elevation group were *H. pylori*-positive, reinforcing the ordered association between infection status and increasing fecal calprotectin category. This increase was statistically significant, whereas median age, age-group distribution, and sex distribution did not differ significantly among the three groups. The comparable demographic characteristics across the groups suggest that the observed association was unlikely to be explained by age or sex alone, although the effects of other potential confounders cannot be excluded.

The association observed in the present study is consistent with the findings of Aksoy et al. (2020), who reported significantly higher fecal calprotectin concentrations in children with biopsy-confirmed *H. pylori* gastritis than in *H. pylori*-negative children [15]. They also found that fecal calprotectin was associated with the histological grade of neutrophil activity in the gastric mucosa. Villalba-Davila et al. (2025) reported a similar pattern in a retrospective pediatric study: mean fecal calprotectin was 241.2 µg/g in *H. pylori*-positive patients compared with 88.1 µg/g in *H. pylori*-negative patients [16]. These studies support an association between *H. pylori*-related gastric inflammation and fecal calprotectin elevation, although both were conducted in pediatric populations and therefore may not be directly generalizable to the wider age range of the present study.

A biologically plausible explanation for this association is the neutrophil-dominant inflammatory response induced by *H. pylori*. Calprotectin is released in large quantities from activated neutrophils and enters the gastrointestinal lumen during inflammatory-cell migration and mucosal injury. Although fecal calprotectin is generally used as a marker of lower gastrointestinal inflammation, active *H. pylori* gastritis can produce substantial neutrophilic infiltration of the gastric mucosa. Calprotectin released during this process may pass through the gastrointestinal tract and contribute to increased fecal concentrations [5, 17]. The progressive increase in *H. pylori* positivity across the fecal calprotectin categories may therefore reflect greater inflammatory activity among infected participants [18].

The inflammatory-marker findings provide further evidence of an inflammatory pattern across the fecal calprotectin categories. Median CRP increased from 1.00 mg/L in the normal group to 2.25 mg/L in the intermediate-elevation group and 3.25 mg/L in the high-elevation group. Median WBC count showed a similar numerical increase from 6.95 × 10⁹/L to 7.69 × 10⁹/L and 8.02 × 10⁹/L, respectively. The overall differences were statistically significant for CRP and WBC count. In contrast, ESR, platelet count, hemoglobin, and ferritin did not differ significantly among the groups. The increase in CRP and WBC count is consistent with the findings of Villalba-Davila et al. (2025), who reported that *H. pylori* infection was associatedwith elevations in fecal calprotectin and systemic inflammatory markers [16]. Sağlam and Civan (2023) also identified changes in neutrophil-related hematological parameters among children with chronic *H. pylori* infection, supporting the presence of a measurable systemic response to gastric inflammation [20]. In a different clinical context, Samant et al. (2015) found that fecal calprotectin correlated significantly with CRP but not with ESR among patients with inflammatory bowel disease [21]. Although the underlying disease differed from that examined in the present study, their findings indicate that fecal calprotectin may correspond more closely with CRP than with ESR during active gastrointestinal inflammation.

The simultaneous increases in fecal calprotectin, CRP, and WBC count may indicate the coexistence of local gastrointestinal inflammation and a modest systemic

inflammatory response. CRP is an acute-phase protein that responds relatively rapidly to inflammatory cytokine stimulation, while WBC count may increase in response to neutrophil activation and recruitment. ESR has slower kinetics and is influenced by age, anemia, plasma proteins, and other non-inflammatory factors [22]. Therefore, active or relatively recent gastrointestinal inflammation may produce detectable increases in CRP and WBC count without a parallel significant difference in ESR. The absence of significant differences in platelet count, hemoglobin, and ferritin may further indicate that the inflammatory process was not sufficiently prolonged or extensive to produce consistent hematological changes across the fecal calprotectin groups. Anemia, altered iron stores, and reactive thrombocytosis are more commonly associated with persistent or extensive inflammatory disease [23].

Among the nutritional and glycemic markers, zinc was the only variable that differed significantly across the fecal calprotectin categories. Median zinc concentration increased from 86.00 µg/dL in the normal group to 93.50 µg/dL in the intermediate-elevation group and then decreased to 85.00 µg/dL in the high-elevation group. This pattern was non-monotonic because zinc did not increase or decrease consistently with fecal calprotectin concentration. Vitamin B12 and HbA1c did not differ significantly among the three groups.

Akcam et al. (2007) similarly found no significant difference in serum zinc between *H. pylori*-positive and *H. pylori*-negative children, although vitamin B12 was significantly lower among infected participants [24]. Shuval-Sudai and Granot (2003) also reported a higher frequency of *H. pylori* seropositivity among adults with vitamin B12 concentrations at the lower end of the normal range [25]. These findings differ partly from the present results, in which vitamin B12 did not vary significantly across fecal calprotectin categories. This difference may be related to the grouping strategy, because the present analysis classified participants according to fecal calprotectin rather than directly comparing nutritional markers according to *H. pylori* status.

The non-monotonic zinc pattern does not support a straightforward dose-response relationship between zinc concentration and gastrointestinal inflammation. Serum zinc is influenced by dietary intake, supplementation, fasting status, serum albumin, inflammatory redistribution, and the timing of sample collection. The statistically significant Kruskal-Wallis result indicates an overall difference among the three groups but does not identify which specific groups differ. The zinc finding should therefore remain exploratory unless it is supported by post hoc pairwise comparisons, such as Dunn's test with an appropriate adjustment for multiple comparisons. The absence of a significant difference in vitamin B12 does not necessarily contradict previous evidence linking *H. pylori* infection with impaired vitamin B12 status. Vitamin B12 depletion may depend on the duration of infection, the extent of gastric atrophy, impaired acid secretion, intrinsic-factor dysfunction, dietary intake, and existing body stores. These processes may develop gradually and may not correspond directly with current fecal calprotectin concentrations. Similarly, the absence of variation in HbA1c is clinically plausible because HbA1c reflects average glycemic exposure over approximately two to three months rather than current gastrointestinal inflammatory activity.

The stool examination results showed that fecal occult blood positivity increased from 3.9% in the normal fecal calprotectin group to 8.0% in the intermediate-elevation group and 20.3% in the high-elevation group. The association between fecal occult blood status and fecal calprotectin category was statistically significant. In contrast, stool RBC and pus-cell positivity did not differ significantly among the three groups.

Shitrit et al. (2007) reported a significant correlation between fecal calprotectin concentration, positive fecal occult blood findings, and abnormal colonic histology in patients undergoing colonoscopy [26]. Their findings support the possibility that the parallel presence of fecal occult blood and elevated calprotectin reflects mucosal inflammation or structural mucosal injury. Vavricka et al. (2018) experimentally demonstrated that gastrointestinal blood exposure can itself increase fecal calprotectin [27]. The increasing frequency of fecal occult blood positivity in the present study may therefore reflect greater mucosal injury or gastrointestinal bleeding among participants with higher fecal calprotectin concentrations. The relationship may also be bidirectional: inflammatory mucosal damage can cause bleeding, while gastrointestinal blood may contribute to a mild increase in fecal calprotectin.

Although gastrointestinal bleeding may contribute to fecal calprotectin elevation, the experimental findings of Vavricka et al. suggest that blood alone would rarely explain concentrations above 250 µg/g [27]. The combination of high fecal calprotectin and fecal occult blood positivity should therefore prompt consideration of an underlying inflammatory or structural gastrointestinal lesion rather than being interpreted as bleeding alone.

The non-significant findings for stool RBC and pus cells should be interpreted cautiously because these tests were available for only a subset of the study population. Stool RBC results were available for 136 participants, while pus-cell results were available for only 64. These smaller samples reduce statistical power and may introduce selection bias if stool microscopy was performed preferentially in participants with specific symptoms or clinical indications. Accordingly, the absence of statistical significance does not establish that stool RBCs or pus cells are unrelated to fecal calprotectin; it indicates only that no association was detected among participants with available results.

Taken together, the findings show a coherent inflammatory pattern in which increasing fecal calprotectin category was accompanied by a higher proportion of *H. pylori*-positive participants, higher CRP concentrations, higher WBC counts, and more frequent fecal occult blood positivity. In contrast, age, sex, ESR, platelet count, hemoglobin, ferritin, vitamin B12, HbA1c, stool RBCs, and stool pus cells did not differ significantly. This pattern suggests that fecal calprotectin elevation was more closely related to active gastrointestinal inflammation and a modest systemic inflammatory response than to demographic characteristics, chronic hematological disturbances, or generalized nutritional and glycemic impairment.

The findings have relevant clinical implications. *H. pylori* infection should be considered as a possible contributor when interpreting elevated fecal calprotectin, particularly in populations with a high infection burden. However, markedly elevated fecal calprotectin should not be attributed automatically to *H. pylori*, especially when accompanied by fecal occult blood positivity. Such a combination may justify further evaluation for inflammatory bowel disease, intestinal infection, medication-related mucosal injury, colorectal lesions, or other organic gastrointestinal conditions. Beyond diagnostic interpretation, the continued spread of bacterial infections and the selective pressure associated with antibiotic use may facilitate the persistence and transmission of resistant strains, potentially limiting the effectiveness of available treatments [28, 29].

Several limitations should be considered when interpreting these findings. The cross-sectional design prevents determination of the temporal or causal relationship between *H. pylori* infection and fecal calprotectin elevation. Information on gastric histological activity, colonoscopic findings, intestinal infections, non-steroidal anti-inflammatory drug use, proton-pump inhibitor use, body mass index, smoking, diet, and nutritional supplementation was not incorporated into the reported comparisons. The wide age range of 4-88 years introduces clinical heterogeneity, particularly because several comparable studies were restricted to children. The limited availability of stool microscopy reduced the power of the analyses involving stool RBCs and pus cells. In addition, the complete absence of *H. pylori*-negative participants in the high-elevation group may create complete separation in conventional regression models. Penalized regression methods may therefore be required if adjusted multivariable analyses are performed.

Despite these limitations, the study has several strengths. It included a relatively large sample of 429 participants and evaluated fecal, systemic inflammatory, hematological, nutritional, glycemic, and stool examination variables within the same population. The ordered increase in *H. pylori* positivity, CRP, WBC count, and fecal occult blood positivity across fecal calprotectin categories provides internally consistent evidence of an inflammatory pattern. The use of clearly defined fecal calprotectin categories also permits clinically interpretable comparisons.

In summary, increasing fecal calprotectin concentration was strongly associated with *H. pylori* positivity and was accompanied by higher CRP concentrations, WBC counts, and fecal occult blood positivity. Collectively, these findings support the presence of active gastrointestinal inflammation with a modest systemic inflammatory component; however, the cross-sectional design cannot establish causality or exclude coexisting intestinal disease. The significant zinc difference was non-monotonic and requires post hoc pairwise analysis before a specific intergroup pattern can be inferred. Prospective studies incorporating endoscopy, histopathology, exclusion of alternative intestinal conditions, and fecal calprotectin measurements before and after *H. pylori* eradication are needed to determine whether the observed association is causal and to distinguish gastric inflammation from coexisting intestinal sources.

4. CONCLUSION

Elevated fecal calprotectin was significantly associated with *H. pylori* positivity, higher CRP and WBC counts, and increased fecal occult blood positivity. These findings indicate a relationship between fecal calprotectin elevation and gastrointestinal inflammatory activity. However, markedly elevated values should not be attributed to *H. pylori* alone without excluding other intestinal causes. Owing to the cross-sectional design, causality cannot be established.

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Data Availability

Available from corresponding author upon request.

Conflict Of Interest

None declared.

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