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Original Article

J Clin Med Res. 2026;18(12):930-937

Helicobacter pylori Infection, Inflammatory Markers, and Extra-Intestinal Manifestations in Inflammatory Bowel Disease: A Cross-Sectional Multivariable Analysis

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Abstract

Background: Extraintestinal manifestations (EIMs) are common in patients with inflammatory bowel disease (IBD), but the factors associated with their occurrence are not well defined. The aim of this study was to examine the association between *Helicobacter pylori* (*H. pylori*) status and EIMs in patients with ulcerative colitis (UC) and Crohn's disease (CD), and to assess the role of inflammatory markers (C-reactive protein, erythrocyte sedimentation rate, and fecal calprotectin).

Methods: This cross-sectional retrospective study included 700 patients with IBD (350 UC, 350 CD) from a single center. *H. pylori* status was determined using stool antigen testing, urea breath testing, rapid urease testing, or histopathology. EIMs were defined as arthritis/arthralgia, uveitis/iritis, erythema nodosum, and pyoderma gangrenosum. Data were analyzed in SPSS 27 using chi-square and Mann–Whitney U tests, and multivariable logistic regression (n = 430 patients with complete data).

Results: *H. pylori* was positive in 267 patients (38.1%), and 289 (41.3%) had at least one EIM. *H. pylori* positivity was more frequent in patients with UC than in those with CD (42.6% and 33.7%, respectively; P = 0.016) and was less frequent among patients with EIMs than among those without EIMs. In the multivariable model, *H. pylori* positivity was independently associated with lower odds of EIMs (adjusted odds ratio (AOR) = 0.388, P < 0.001), whereas elevated CRP was associated with higher odds (AOR = 2.43, P < 0.001). The Nagelkerke R^2 was 0.213.

Conclusion: In this cross-sectional study, *H. pylori* positivity was associated with a lower likelihood of EIMs in IBD, independent of disease type, activity, treatment, and inflammatory markers. A causal relationship cannot be established, and prospective studies are needed.

Keywords: Inflammatory bowel disease; *Helicobacter pylori*; Extraintestinal manifestations; Crohn's disease; Ulcerative colitis; Immune modulation; Multivariable analysis, C-reactive protein

Introduction

Inflammatory bowel disease (IBD) is a chronic, immune-mediated condition marked by recurrent inflammation of the gastrointestinal tract, arising from a combination of genetic susceptibility, environmental exposures, gut microbiota alterations, and immune dysregulation [1]. Although the gut remains the primary site of disease, extraintestinal involvement is increasingly recognized. Approximately 40–50% of patients with IBD develop one or more extraintestinal manifestations (EIMs) during the course of their disease [2]. These complications affect multiple organ systems, including the musculoskeletal, dermatological, ocular, and hepatobiliary systems, and are associated with reduced quality of life, higher healthcare utilization, and more complicated treatment decisions [3–5]. Some EIMs track closely with intestinal disease activity, whereas others follow a relatively independent course, reflecting distinct and sometimes overlapping pathogenic mechanisms [2, 5]. These manifestations have been linked to systemic immune dysfunction, particularly pathways involving interleukin-23 (IL-23)/T helper 17 (Th17) and tumor necrosis factor-alpha (TNF-α) [6]. The balance between Th17 cells and regulatory T cells also plays an important role in extraintestinal inflammation. Shared genetic susceptibility loci between IBD and other immune-mediated diseases further support the involvement of systemic inflammatory pathways, rather than local intestinal pathology alone, in the development of these manifestations [1, 7].

There has also been growing interest in how chronic microbial exposure shapes systemic immunity. *Helicobacter pylori* (*H. pylori*), a Gram-negative organism that colonizes the gastric mucosa, remains one of the most prevalent chronic infections worldwide, particularly in low- and middle-income countries [8]. Traditionally regarded primarily as a gastric pathogen, *H. pylori* is now recognized as having broader immunomodulatory effects, potentially through prolonged

Manuscript submitted September 3, 2026, accepted November 10, 2026
Published online November 27, 2026

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doi: https://doi.org/10.14740/jocmr6723
Journal of Clinical Medicine Research
1918-3003 (print), 1918-3011 (online)

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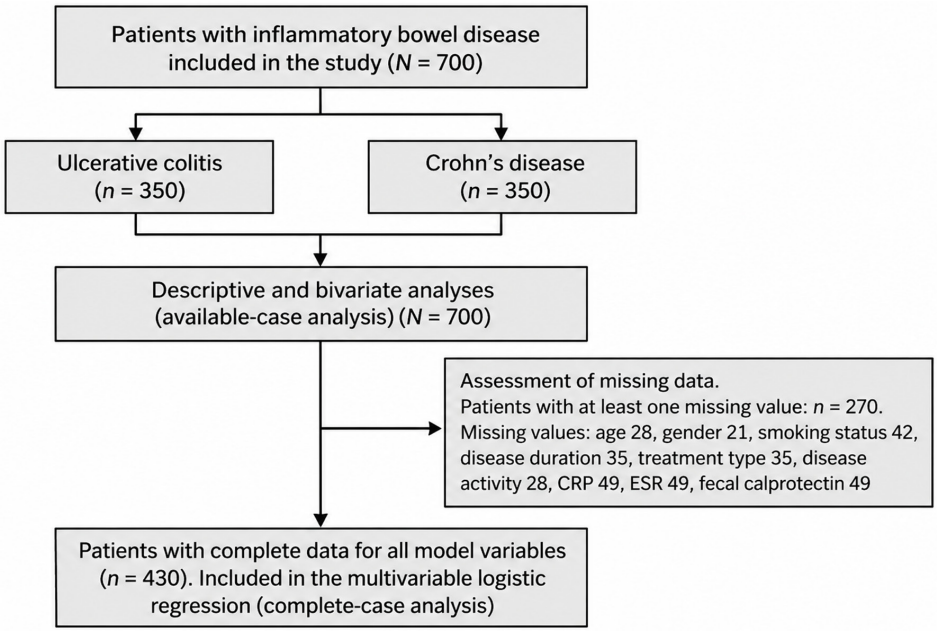


Figure 1. Flow diagram illustrating participant selection, missing data assessment, and inclusion in descriptive, bivariate, and multivariable analyses.

host–microbe interactions that influence immune tolerance. Epidemiological studies and meta-analyses have reported an association between *H. pylori* carriage and reduced IBD risk [9, 10]. However, this evidence largely concerns disease susceptibility rather than disease behavior after IBD has been established. Whether *H. pylori* influences the clinical phenotype of established IBD, particularly the burden of EIMs, has received considerably less attention [5]. Despite growing recognition of a possible immunological link between *H. pylori* and IBD, the relationship between *H. pylori* status and EIM burden in patients with established IBD remains insufficiently investigated. This study therefore examined the association between *H. pylori* status and both the presence and burden of EIMs in patients with UC and CD using multivariable analysis.

Materials and Methods

Study design and population

This retrospective cross-sectional study included adult patients (≥ 18 years) with a confirmed diagnosis of UC or CD who attended the gastroenterology outpatient clinic or were admitted to the study center between January 2021 and September 2025. A total of 700 patients with documented *H. pylori* results were included in the descriptive and bivariate analyses. *H. pylori* status was determined using stool antigen testing, urea breath testing, rapid urease testing, or histopathology. The multivariable analysis was restricted to the 430 patients with complete data for all variables included in the model. Patients were excluded if their *H. pylori* results were unavailable or inconclusive, if they had a gastrointestinal malignancy, or if they had a major systemic autoimmune disease other than IBD (Fig. 1).

Sample size

The study population was identified retrospectively from the hospital's electronic medical record system over the period from January 2021 to September 2025. A total of 700 eligible patients were identified, comprising 350 patients with UC and 350 with CD. The available sample was used for descriptive and bivariate analyses, while complete-case data were used for the multivariable analysis.

Inclusion and exclusion criteria

Eligible patients were adults (≥ 18 years) with a definitive diagnosis of UC or CD based on standard clinical, endoscopic, radiological, and histological criteria and a documented *H. pylori* result. Patients with unavailable or inconclusive *H. pylori* results, gastrointestinal malignancy, or a major systemic autoimmune disease other than IBD were excluded.

Patients with missing values for individual clinical or laboratory variables were retained in descriptive and bivariate analyses when the relevant data were available. However, patients with missing data for any variable included in the multivariable model were excluded from the complete-case analysis.

Data collection

Data were extracted retrospectively from the electronic medi-

cal records of eligible patients diagnosed with UC or CD between January 2021 and September 2025. The collected variables included demographic characteristics (age and gender), clinical characteristics (IBD type, disease duration, smoking status, treatment type, and disease activity), laboratory parameters (C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and fecal calprotectin), *H. pylori* status, and EIMs. *H. pylori* status was classified as positive or negative according to the test result documented in the medical record. The diagnostic methods included stool antigen testing, urea breath testing, rapid urease testing, and histopathological examination. However, the specific testing method was not consistently recorded in a structured format and therefore could not be analyzed separately. Information regarding previous *H. pylori* eradication treatment and the timing of testing in relation to eradication therapy was also unavailable.

EIMs were classified according to the European Crohn's and Colitis Organisation (ECCO)/Vavricka classification and included arthritis/arthralgia, erythema nodosum, uveitis/iritis, and pyoderma gangrenosum. The primary outcome was the presence of at least one of these EIMs. The number of true EIMs per patient was also recorded and analyzed as a count. Perianal complications, including anal fissures, perianal fistulas, perianal abscesses, and other fistulizing disease, were recorded separately and were not classified as true EIMs. EIMs were recorded as documented in the medical records up to the time of data extraction. However, the available records did not consistently distinguish historical from current manifestations or establish their temporal relationship with *H. pylori* testing. CRP, ESR, and fecal calprotectin were collected as laboratory measures of inflammation. For categorical analyses, elevated CRP was defined as greater than 5 mg/L, elevated ESR as greater than 30 mm/h, and elevated fecal calprotectin as greater than 250 µg/g. These biomarkers were also retained as continuous variables where appropriate.

Statistical analyses

Data were analyzed using IBM SPSS Statistics, version 27. Missing data were present for age (n = 28), gender (n = 21), smoking status (n = 42), disease duration (n = 35), treatment type (n = 35), disease activity (n = 28), and CRP, ESR, and fecal calprotectin (n = 49 each). Descriptive and bivariate analyses used all available data for each variable, and percentages were calculated based on the number of patients with available data. The multivariable model was based on a complete-case analysis (n = 430; 270 patients had at least one missing value). Categorical variables are presented as frequencies and percentages, whereas continuous variables are presented as median (interquartile range) and mean ± standard deviation. The *H. pylori*-positive and *H. pylori*-negative groups were compared using the Mann–Whitney U test for continuous variables and the Pearson chi-square test for categorical variables. Odds ratios and 95% confidence intervals were calculated for 2 × 2 comparisons. Multivariable logistic regression was used to identify factors associated with the presence of any true EIM, and results are presented as adjusted odds ratios (AORs) with 95% confidence intervals. The model included *H. pylori* status, CRP, ESR, fecal calprotectin, disease type, gender, treatment type, disease activity, smoking status, age, and disease duration. The reference categories were *H. pylori*-negative status, normal biomarker levels, UC, male gender, conventional treatment, mild disease activity, and never-smoking status. Collinearity among the three inflammatory markers was assessed using variance inflation factors. A two-sided P value < 0.05 was considered statistically significant.

Ethical considerations

The study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration. The study was approved by the Institutional Review Board (IRB) of Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia (IRB Number: 2025-01-090), and the requirement for informed consent was waived because of the retrospective nature of the study.

Results

Baseline categorical characteristics of the study population

The baseline characteristics of the 700 patients (350 with UC and 350 with CD) are presented in Table 1. Men comprised the majority of the study population, and conventional therapy was the most common treatment type. Most patients had never smoked, while moderate disease activity was the most frequently reported. *H. pylori* infection was identified in a proportion of patients, and arthritis/arthralgia was the most frequent true EIM. Current smoking was more common in patients with CD, whereas *H. pylori* positivity and erythema nodosum were more frequent in patients with UC. Overall EIM prevalence, gender, and treatment type did not differ significantly between the disease groups.

Association between *H. pylori* status and clinical and disease characteristics

As shown in Table 2, *H. pylori* positivity was not significantly associated with gender, treatment type, or disease activity. However, significant associations were observed with disease type, smoking status, and the presence of true EIM. *H. pylori* positivity was more frequent in patients with UC and among ex-smokers. The presence of true EIM was less frequent among *H. pylori*-positive patients than among *H. pylori*-negative patients.

Comparison of continuous variables by *H. pylori* status

As presented in Table 3, age, disease duration, CRP, ESR, and fecal calprotectin did not differ significantly between *H. pylori*-positive and *H. pylori*-negative patients. However, the number of true EIMs per patient was significantly lower

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Table 1. Baseline Categorical Characteristics of the Study Population

Variable	Category	Total (N = 700)	UC (n = 350)	CD (n = 350)
Gender	Male	365 (53.8%)	189 (55.4%)	176 (52.1%)
	Female	314 (46.2%)	152 (44.6%)	162 (47.9%)
Treatment type	Conventional	331 (49.8%)	169 (50.4%)	162 (49.1%)
	Biologic	158 (23.8%)	83 (24.8%)	75 (22.7%)
	Both	176 (26.5%)	83 (24.8%)	93 (28.2%)
Smoking status	Never	329 (50.0%)	195 (59.5%)	134 (40.6%)
	Current	169 (25.7%)	54 (16.5%)	115 (34.8%)
	Ex-smoker	160 (24.3%)	79 (24.1%)	81 (24.5%)
Disease activity	Mild	223 (33.2%)	121 (36.6%)	102 (29.9%)
	Moderate	303 (45.1%)	145 (43.8%)	158 (46.3%)
	Severe	146 (21.7%)	65 (19.6%)	81 (23.8%)
H. pylori status	Positive	267 (38.1%)	149 (42.6%)	118 (33.7%)
	Negative	433 (61.9%)	201 (57.4%)	232 (66.3%)
Any true EIM	Yes	289 (41.3%)	138 (39.4%)	151 (43.1%)
	No	411 (58.7%)	212 (60.6%)	199 (56.9%)
Individual EIM type	Arthritis/arthralgia	207 (29.6%)	99 (28.3%)	108 (30.9%)
	Erythema nodosum	92 (13.1%)	60 (17.1%)	32 (9.1%)
	Uveitis/iritis	75 (10.7%)	37 (10.6%)	38 (10.9%)
	Pyoderma gangrenosum	35 (5.0%)	15 (4.3%)	20 (5.7%)

CD: Crohn's disease; EIM: extraintestinal manifestation; UC: ulcerative colitis.

among *H. pylori*-positive patients.

Multivariable logistic regression analysis of factors associated with any EIM

In the multivariable logistic regression model (Table 4), *H. pylori* positivity was independently associated with lower odds of true EIM. Elevated CRP and severe disease activity compared with mild activity were associated with higher odds of EIM. ESR, fecal calprotectin, disease type, gender, treatment type, smoking status, age, and disease duration were not independently associated with EIM. The overall model was statistically significant, with modest explanatory

Table 2. Association Between *H. pylori* Status and Clinical and Disease Characteristics

Variable	Category	*H. pylori* positive	*H. pylori* negative	Chi-square	Odds ratio (95% CI)	P-value
Gender	Male	134	231	0.434	0.90 (0.66–1.23)	0.510
	Female	123	191			
Any true EIM	Yes	84	205	16.540	0.51 (0.37–0.70)	< 0.001*
	No	183	228			
Treatment type	Biologic	56	102	0.685	—	0.710
	Conventional	130	201			
	Both	68	108			
Disease type	Crohn's disease	118	232	5.819	0.69 (0.50–0.93)	0.016*
	Ulcerative colitis	149	201			
Smoking status	Current	50	119	7.724	—	0.021*
	Ex-smoker	71	89			
	Never	122	207			
Disease activity	Mild	85	138	1.205	—	0.547
	Moderate	120	183			
	Severe	50	96			

*P-value indicates statistical significance (P < 0.05; Pearson chi-square test). CI: confidence interval; EIM: extraintestinal manifestation.

Table 3. Comparison of Continuous Variables by *H. pylori* Status

Variable	*H. pylori* negative	*H. pylori* positive	Mann–Whitney U	P-value
Age (years)	41.0 (30.5–50.5); 40.7 ± 12.8	43.0 (34.0–51.0); 42.6 ± 13.1	49,184.5	0.090
Disease duration (years)	6.3 (3.9–10.0); 7.6 ± 5.2	7.0 (4.3–9.7); 7.7 ± 4.5	48,561.5	0.201
C-reactive protein (mg/L)	5.8 (3.2–10.0); 7.8 ± 6.9	5.8 (3.0–11.2); 7.8 ± 6.8	50,131.5	0.919
Erythrocyte sedimentation rate (mm/h)	32.0 (20.0–44.0); 32.2 ± 16.1	31.0 (21.0–44.0); 32.6 ± 16.6	49,474.0	0.911
Calprotectin (µg/g)	305.0 (167.0–501.0); 384.2 ± 280.1	292.5 (148.0–487.8); 362.4 ± 282.7	52,996.0	0.219
Number of true EIMs[a]	0.0 (0.0–1.0); 0.7 ± 0.9	0.0 (0.0–1.0); 0.4 ± 0.7	68,113.5	< 0.001*

*P-value indicates statistical significance (P < 0.05; Mann–Whitney U test). [a]True EIMs include arthritis/arthralgia, uveitis/iritis, erythema nodosum, and pyoderma gangrenosum. Data are presented as median (IQR); mean ± SD (Mann–Whitney U test). EIM: extraintestinal manifestation; IQR: interquartile range; SD: standard deviation.

and classification performance.

Distribution of individual EIM types and local complications by disease type and *H. pylori* status

As shown in Table 5, *H. pylori* positivity was significantly associated with lower frequencies of arthritis/arthralgia, erythema nodosum, and uveitis/iritis. No significant association was observed for pyoderma gangrenosum. Among local complications, perianal fistulas and abscesses were more frequent in patients with CD than in those with UC. These complications were reported separately and were not included in the true EIM definition.

Table 4. Multivariable Logistic Regression Analysis of Factors Associated With Any Extraintestinal Manifestation

Variable	Category	B	SE	Wald χ^2	P-value	Adjusted OR (Exp(B))	95% CI for OR
H. pylori status	Negative	—					
	Positive	−0.948	0.241	15.49	< 0.001***	0.388	0.24–0.62
High CRP	No	—					
	Yes	0.887	0.245	13.06	< 0.001***	2.43	1.50–3.93
High ESR	No	—					
	Yes	−0.095	0.273	0.12	0.728	0.91	0.53–1.55
High calprotectin	No	—					
	Yes	0.245	0.299	0.67	0.413	1.28	0.71–2.30
Disease type	UC	—					
	CD	0.007	0.229	0.001	0.977	1.01	0.64–1.58
Gender	Male	—					
	Female	−0.048	0.221	0.05	0.827	0.95	0.62–1.47
Treatment type	Conventional	Reference				1.00	—
	Biologic	0.489	0.294	2.77	0.096	1.63	0.92–2.90
	Both	0.510	0.271	3.53	0.060	1.66	0.98–2.83
Disease activity	Mild	Reference				1.00	—
	Moderate	0.492	0.353	1.94	0.163	1.64	0.82–3.27
	Severe	0.942	0.477	3.90	0.048*	2.56	1.01–6.53
Smoking status	Never	Reference				1.00	—
	Current	0.212	0.270	0.61	0.434	1.24	0.73–2.10
	Ex-smoker	−0.058	0.273	0.05	0.831	0.94	0.55–1.61
Age (per year)	-	−0.007	0.009	0.57	0.452	0.99	0.98–1.01
Disease duration (per year)	-	−0.002	0.021	0.006	0.937	1.00	0.96–1.04

*P < 0.05; ***P< 0.001 (Pearson chi-square test). Model statistics: Omnibus χ^2 = 73.255, df = 14, P < 0.001; −2 Log likelihood = 498.424; Cox & Snell R^2 = 0.157; Nagelkerke R^2 = 0.213; overall classification accuracy = 68.4% (n = 430, complete-case analysis). CD: Crohn's disease; CI: confidence interval; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; SE: standard error; UC: ulcerative colitis.

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Table 5. Distribution of Individual EIM Types and Local Complications by Disease Type, With *H. pylori* Association

Category	Type	Total (N = 700)	UC (n = 350)	CD (n = 350)	*H. pylori*+ (n = 267)	*H. pylori*− (n = 433)	χ^2	P value
True EIM	Arthritis/arthralgia	207 (29.6%)	99 (28.3%)	108 (30.9%)	62 (23.2%)	145 (33.5%)	7.87	0.005
	Erythema nodosum	92 (13.1%)	60 (17.1%)	32 (9.1%)	20 (7.5%)	72 (16.6%)	11.29	< 0.001
	Uveitis/iritis	75 (10.7%)	37 (10.6%)	38 (10.9%)	17 (6.4%)	58 (13.4%)	7.81	0.005
	Pyoderma gangrenosum	35 (5.0%)	15 (4.3%)	20 (5.7%)	9 (3.4%)	26 (6.0%)	1.89	0.169
Local complication	Anal fissure	75 (10.7%)	37 (10.6%)	38 (10.9%)	—	—	—	—
	Perianal fistula	68 (9.7%)	18 (5.1%)	50 (14.3%)	—	—	—	—
	Perianal abscess	47 (6.7%)	14 (4.0%)	33 (9.4%)	—	—	—	—
	Other fistulizing disease	16 (2.3%)	8 (2.3%)	8 (2.3%)	—	—	—	—

CD: Crohn's disease; EIM: extraintestinal manifestation; UC: ulcerative colitis.

Univariable associations between inflammatory biomarkers and EIM status

In unadjusted analyses (Table 6), elevated CRP, ESR, and fecal calprotectin were each significantly associated with true EIM. Variance inflation factors indicated no concerning multicollinearity among the inflammatory markers. In the multivariable model, only CRP remained independently associated with EIM.

Discussion

In this cross-sectional study of 700 patients with IBD, *H. pylori* positivity was independently associated with lower odds of EIMs after adjustment for disease type, activity, treatment, smoking, and inflammatory markers, whereas elevated CRP was associated with higher odds. The prevalence of EIMs (41.3%) was in line with the 40–50% reported previously [2, 11]. These findings support the view that IBD is a systemic disease and that EIMs remain an important source of disease burden, quality-of-life impairment, and treatment complexity [3, 4]. The finding of an inverse association with *H. pylori* is consistent with meta-analyses reporting a lower prevalence of *H. pylori* infection in patients with IBD, including pediatric cohorts [12, 13]; however, those studies addressed susceptibility to IBD rather than the extraintestinal phenotype of established disease. *H. pylori* positivity was more frequent in patients with UC than in those with CD (42.6% and 33.7%, respectively; P = 0.016), while disease type was not independently associated with EIMs in the adjusted model. This represents a descriptive difference in the present cohort. The reason for this difference is unclear from the available data and may reflect variations in patient characteristics or treatment exposure between the two disease groups. These possibilities warrant further investigation in future studies.

Elevated CRP was independently associated with higher odds of EIMs, whereas ESR and fecal calprotectin were not independently associated with EIMs after adjustment for other factors. Some EIMs follow a course partly independent of intestinal inflammation [2, 5], and markers of luminal or mucosal inflammatory activity do not always correspond with extraintestinal disease activity. The association with CRP may therefore indicate a link between EIMs and systemic inflammatory status rather than luminal inflammation alone. Known genetic associations between IBD and other immune-mediated diseases, together with shared inflammatory pathways such as the IL-23/Th17 axis, suggest that microbial exposures may modulate systemic immune responses and influence EIMs beyond intestinal inflammation [6, 7]. This study has several strengths, including a relatively large and well-balanced sample of 700 patients, comprising equal numbers of patients with UC and CD, and multivariable modeling that accounted for demographic, clinical, treatment, and inflammatory biomarker factors. However, several limitations should be acknowledged. First, the retrospective cross-sectional design cannot establish temporality or rule out reverse causality between *H. pylori* infection and EIMs. Second, information on previous *H. pylori* infection and eradication therapy was not consistently available in the electronic medical records and could not be included in the analysis. Previous eradication therapy may influence gut microbiota composition and systemic immune responses, representing a potential unmeasured confounder. Third, different diagnostic methods were used to determine *H. pylori* status, and the specific diagnostic modality was not consistently documented for individual patients. This may have introduced variability in diagnostic sensitivity and specificity. Furthermore, it was not possible to determine

Table 6. Univariable (Unadjusted) Associations Between Inflammatory Biomarkers and True EIM Status

Biomarker	Unadjusted OR	χ^2	P value
C-reactive protein (mg/L)	2.77 (1.99–3.87)	35.95	< 0.001***
Erythrocyte sedimentation rate (mm/h)	2.11 (1.53–2.91)	20.44	< 0.001***
Fecal calprotectin (µg/g)	2.49 (1.78–3.47)	28.59	< 0.001***

***P < 0.001 (statistically significant). EIM: extraintestinal manifestation; OR: odds ratio.

whether *H. pylori* testing was performed at initial diagnosis or following previous eradication therapy. Consequently, some patients with successful prior eradication may have been classified as *H. pylori*-negative, potentially affecting the observed association. Fourth, *H. pylori* virulence factors, particularly CagA and VacA, were not evaluated, although they may influence host immune responses. Hepatobiliary involvement could not be assessed because the relevant information was unavailable in the dataset. Finally, residual confounding from unmeasured environmental and microbial factors cannot be excluded. Missing data were present for several variables, and the multivariable model was restricted to the 430 patients with complete data, which may have reduced statistical power and introduced selection bias. Despite these limitations, the findings indicate an association between *H. pylori* positivity and lower odds of EIMs among patients with IBD. Prospective longitudinal studies incorporating previous eradication history and *H. pylori* virulence factors are needed to further investigate this association and clarify the underlying mechanisms.

Conclusion

In this cross-sectional study of patients with IBD, *H. pylori* positivity was independently associated with lower odds of EIMs, whereas elevated CRP was associated with higher odds. Given the retrospective cross-sectional design and the lack of information on previous *H. pylori* eradication and bacterial virulence factors, these findings are hypothesis-generating and do not establish causation. Prospective studies incorporating eradication history and virulence factors are needed to further investigate these associations.

Acknowledgments

None to declare.

Financial Disclosure

This study was not supported by any sponsor or funder.

Conflict of Interest

The authors declare no conflict of interest for this article.

Informed Consent

The requirement for informed consent was waived due to the retrospective nature of the study.

Author Contributions

AD contributed to the study conception and design, data collection, and data extraction; JM performed the statistical analysis and interpretation of the data; JM and AD each wrote and critically revised the manuscript. Both authors contributed equally and read and approved the final manuscript.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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