Fecal Calprotectin Level is Nonlinearly Associated with GI Pathogen Detection in Patients with and without Inflammatory Bowel Disease

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Abstract

Introduction: Fecal calprotectin (FCP) is an inflammatory marker frequently used to monitor inflammatory bowel disease (IBD) activity, but it can also be elevated in gastrointestinal infections. The impact of infections on FCP level in people with IBD has not been well described across pathogens. The objective of our study was to quantify the relationship between FCP levels and lab-confirmed infections in people with and without IBD.
Methods: We performed a retrospective cohort study at a tertiary-care referral center of inpatient and outpatient encounters during which FCP and gastrointestinal pathogen polymerase-chain reaction (GI PCR) testing were conducted. Using non-parametric tests and quantile regression, we compared FCP levels between individuals with and without IBD and with and without pathogen detection.
Results: There were 3,347 encounters with FCP and GI PCR testing from 2,780 unique individuals between August 1, 2016 and February 17, 2022. Overall, 1819 (53.5%) encounters were individuals with IBD (n=1,819). Pathogens were detected in 757 encounters (22.3%). There was no significant difference in pathogen detection or pathogen type between groups with and without IBD (p>0.9). The median FCP was 46 mg/kg in individuals without IBD and 265 mg/kg in those with IBD (p<0.001). Among individuals without IBD, the median FCP was significantly elevated when a pathogen was detected (64 vs. 41 mg/kg, p=0.0003, Figure), but FCP was not significantly elevated among those with IBD when a pathogen was detected (299 vs. 255 mg/kg, p=0.207). After adjusting for age and IBD status in quantile regression, pathogen detection was only significantly associated with higher FCP in the lower two quartiles, though IBD remained significantly associated with higher FCP at all levels (p>0.001). After adjusting for IBD and age, FCP was significantly associated with detection of bacterial pathogens and multiple pathogens in the lower two quartiles.
Discussion: Pathogen detection by GI PCR is associated with elevated FCP, though this relationship is nonlinear and varies by IBD status. Even after stratifying by IBD status, there is significant variability in FCP, suggesting that factors in addition to infection may be playing a role, including potentially measurement error, or a greater immune reaction to pathogen infection in IBD leading to mild flares. Our findings indicate that FCP may be an adjunct to, but not a substitute for stool pathogen testing.

Introduction

- Fecal calprotectin (FCP) is a common laboratory marker of gut inflammation in inflammatory bowel disease (IBD).
- FCP be elevated in the presence of infections.
- The association between FCP levels and infections in patients with IBD has not been well-described across pathogen types.
- GI infections are common in patients with IBD, especially during flares.
- Because GI infections can affect FCP, and individuals with IBD may be at greater risk for GI infections, there is potential for misinterpretation of FCP results.
- The purpose of this study was to determine how stool FCP is affected by the presence of GI pathogens in individuals with and without IBD.

Methods and Materials

- Design: retrospective cohort study
- Location: single Midwestern tertiary-care referral center
- Eligible encounters: Any inpatient and outpatient encounters (August 1, 2016 to February 17, 2022) with FCP and GI PCR testing
- Ethics: Study approved by UM IRB
- Exposure: IBD diagnosis based on ICD-9 or ICD-10 codes
- Primary outcome: FCP level in individuals with and without IBD
- Analytic methods: non-parametric tests and quantile regression in R.

Table 1. Characteristics of encounters in people with and without IBD who had fecal calprotectin and gastrointestinal pathogen testing.

Variable	Overall N = 3,347[1]	IBD diagnosis		p-value[2]
		No IBD N = 1,528[1]	IBD N = 1,819[1]	
Fecal calprotectin (mg/kg)	107 (31, 498)	46 (24, 168)	265 (56, 903)	<0.001
Pathogen detected	744 (22%)	340 (22%)	404 (22%)	>0.99
Age (years)	39 (25, 57)	41 (23, 61)	38 (26, 55)	0.02
Sex				<0.001
Female	2,013 (60%)	988 (65%)	1,025 (56%)	
Male	1,333 (40%)	540 (35%)	793 (44%)	
Race				0.13
African American	332 (9.9%)	135 (8.8%)	197 (11%)	
American Indian or Alaska Native	5 (0.1%)	3 (0.2%)	2 (0.1%)	
Asian	92 (2.8%)	51 (3.3%)	41 (2.3%)	
Caucasian	2,768 (83%)	1,277 (84%)	1,491 (82%)	
Native Hawaiian and Other Pacific Islander	1 (<0.1%)	1 (<0.1%)	0 (0%)	
Other	113 (3.4%)	49 (3.2%)	64 (3.5%)	
Patient Refused	18 (0.5%)	5 (0.3%)	13 (0.7%)	
Unknown	16 (0.5%)	7 (0.5%)	9 (0.5%)	
Ethnicity				0.35
Hispanic or Latino	89 (2.7%)	49 (3.2%)	40 (2.2%)	
Non-Hispanic or Latino	3,193 (96%)	1,449 (95%)	1,744 (96%)	
Patient Refused	22 (0.7%)	10 (0.7%)	12 (0.7%)	
Unknown	39 (1.2%)	18 (1.2%)	21 (1.2%)	
Inpatient encounter	1,435 (43%)	523 (34%)	912 (50%)	<0.001

[1] Median (IQR); n (%) ; [2] Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

Results

Table 2. Pathogens detected in encounters with people with and without IBD who had fecal calprotectin and gastrointestinal pathogen PCR testing.

Pathogen	Overall, N = 3,347[1]	IBD diagnosis		p-value[2]
		No IBD, N = 1,528[1]	IBD, N = 1,819[1]	
Any pathogen	744 (22%)	340 (22%)	404 (22%)	>0.9
Any bacterial pathogen	675 (20%)	301 (20%)	374 (21%)	0.5
Campylobacter	31 (0.9%)	14 (0.9%)	17 (0.9%)	>0.9
Clostridium difficile	401 (12%)	177 (12%)	224 (12%)	0.5
Escherichia coli	253 (7.6%)	115 (7.5%)	138 (7.6%)	>0.9
P. shigelloides	13 (0.4%)	3 (0.2%)	10 (0.5%)	0.1
Salmonella	12 (0.4%)	7 (0.5%)	5 (0.3%)	0.4
Vibrio	6 (0.2%)	1 (<0.1%)	5 (0.3%)	0.2
Yersinia	9 (0.3%)	4 (0.3%)	5 (0.3%)	>0.9
Any viral pathogen	84 (2.5%)	45 (2.9%)	39 (2.1%)	0.14
Adenovirus	8 (0.2%)	5 (0.3%)	3 (0.2%)	0.5
Astrovirus	6 (0.2%)	3 (0.2%)	3 (0.2%)	>0.9
Norovirus	55 (1.6%)	30 (2.0%)	25 (1.4%)	0.2
Rotavirus	1 (<0.1%)	1 (<0.1%)	0 (0%)	0.5
Sapovirus	15 (0.4%)	7 (0.5%)	8 (0.4%)	>0.9
Any parasite	16 (0.5%)	10 (0.7%)	6 (0.3%)	0.2
Cryptosporidum	7 (0.2%)	2 (0.1%)	5 (0.3%)	0.5
Cyclospora	4 (0.1%)	4 (0.3%)	0 (0%)	0.043
Giardia	5 (0.1%)	4 (0.3%)	1 (<0.1%)	0.2

[1] Median (IQR); n (%) ; [2] Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

Figure 1. Fecal calprotectin levels by stool pathogen testing result and IBD diagnosis.

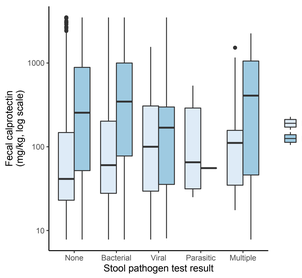
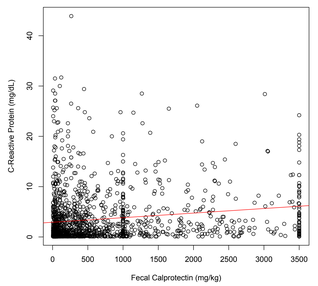


Figure 2. Fecal calprotectin and serum C-reactive protein levels from encounters with fecal calprotectin and gastrointestinal pathogen testing. Circle=encounter. Red line =unadjusted linear best fit



Results

- Overall, 3,347 encounters with FCP and GI PCR testing from 2,780 unique individuals
- There was no significant difference in the incidence of pathogen detection or pathogen types detected between groups with and without IBD (p>0.9).
- The median FCP was 46 mg/kg in individuals without IBD and 265 mg/kg in those with IBD (p<0.001).
- Among individuals without IBD, the median FCP was significantly elevated when a pathogen was detected (64 vs. 41 mg/kg, p=0.0003).
- FCP was not significantly elevated among those with IBD when a pathogen was detected (299 vs. 255 mg/kg, p=0.207).
- FCP and CRP were weakly correlated (rho=0.30, p<0.001).

Discussion

- FCP levels were not consistently associated with pathogen detection in individuals with IBD.
- FCP exhibits a nonlinear association with pathogen detection across different quantiles of its distribution.
- Even after controlling for IBD and inpatient hospitalization, there was significant variability in FCP, suggesting that factors in addition to infection may be playing a role.

Conclusions

- Clinicians should use FCP as adjunct to GI pathogen testing when there is suspicion for IBD or IBD flare, rather than as a substitute.
- FCP suggests immunologic differences in inflammatory pathway activation between people with and without IBD.

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References

1. Axelrad JE, Joelson A, Nobel YR, et al. Enteric infection in relapse of inflammatory bowel disease: the utility of stool microbial PCR testing. Inflamm Bowel Dis. 2017;23:1034–9.
2. Chen CC, Huang JL, Chang CJ, Kong MS. Fecal calprotectin as a correlative marker in clinical severity of infectious diarrhea and usefulness in evaluating bacterial or viral pathogens in children. J Pediatr Gastroenterol Nutr. 2012 Nov;55(5):541-7. doi: 10.1097/MPG.0b013e318262a718. PMID: 22699836.
3. Mosli MH, Zou G, Garg SK, Feagan SG, MacDonald JK, Chande N, Sandborn WJ, Feagan BG. C-Reactive Protein, Fecal Calprotectin, and Stool Lactoferrin for Detection of Endoscopic Activity in Symptomatic Inflammatory Bowel Disease Patients: A Systematic Review and Meta-Analysis. Am J Gastroenterol. 2015 Jun;110(6):802-19; quiz 820. doi: 10.1038/ajg.2015.120. Epub 2015 May 12. PMID: 25964225.
4. Peretz, A., Tkhawkho, L., Pastukh, N. *et al.* Correlation between fecal calprotectin levels, disease severity and the hypervirulent ribotype 027 strain in patients with *Clostridium difficile* infection. *BMC Infect Dis* **16**, 309 (2016). https://doi.org/10.1186/s12879-016-1618-8