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# Correlation between Fecal Calprotectin Level and Presence of Esophageal Varices in Patients with Liver Cirrhosis

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## Abstract

# Background

Esophageal varices are a serious complication of portal hypertension in liver cirrhosis, and upper gastrointestinal endoscopy — the diagnostic gold standard — is invasive and resource-intensive. Fecal calprotectin, a neutrophil-derived marker of intestinal inflammation, has been proposed as a non-invasive marker of portal-hypertension-related gut changes.

# Aim

To evaluate fecal calprotectin as a non-invasive predictor of the presence and severity of esophageal varices in patients with HCV-related liver cirrhosis.

## Introduction

Esophageal varices are among the most serious complications of portal hypertension in patients with liver cirrhosis, carrying a substantial risk of variceal hemorrhage and contributing significantly to cirrhosis-related morbidity and mortality [1, 2]. Their prevalence rises with the severity of liver disease: varices are present in only a minority of patients with well-compensated (Child-Pugh A) cirrhosis, but in the majority of those with decompensated (Child-Pugh B/C) disease, and roughly 8% of cirrhotic patients develop new or progressively larger varices each year [2].

Upper gastrointestinal endoscopy remains the diagnostic gold standard for detecting and grading esophageal varices, owing to its high sensitivity and specificity. However, it is invasive, costly, requires sedation and specialized expertise, and is poorly tolerated by many patients — limitations that are especially pronounced in resource-limited settings, where universal endoscopic screening of all cirrhotic patients is often impractical [1, 2]. This has driven sustained interest in non-invasive alternatives that could triage patients toward or away from endoscopy.

A range of non-invasive markers has been explored for this purpose, including platelet count, spleen diameter, the platelet count/spleen diameter ratio, and composite scores such as APRI, FIB-4, and the platelet–albumin–bilirubin (PALBI) score, with reported areas under the ROC curve (AUC) typically in the 0.7–0.85 range [2, 3]. While useful, none has achieved sufficient accuracy or reproducibility to fully replace endoscopic screening, leaving room for additional non-invasive candidates that capture different aspects of the underlying pathophysiology.

Fecal calprotectin is a calcium- and zinc-binding protein released predominantly by neutrophils and is a well-established, widely available marker of intestinal mucosal inflammation, most familiar from its role in distinguishing inflammatory bowel disease from irritable bowel syndrome [4]. In liver cirrhosis, portal hypertension is thought to promote intestinal mucosal congestion, increased gut permeability, dysbiosis,

and bacterial translocation across the gut–liver axis [4, 5]; fecal calprotectin has therefore been proposed as an indirect marker of this gut-barrier disruption, sometimes described as an"ESR of the intestine"[4]. Elevated fecal (and plasma or ascitic) calprotectin has been linked in prior work to hepatic encephalopathy, spontaneous bacterial peritonitis, and adverse outcomes in advanced chronic liver disease [4, 5, 6], suggesting it may also track the severity of portal hypertension and its complications, including esophageal varices.

The most directly comparable prior work is an Egyptian cohort study of 250 participants (100 HCV-cirrhotic patients with esophageal varices, 100 HCV-cirrhotic patients without varices, and 50 healthy controls), which found significantly higher fecal calprotectin in patients with varices and reported a cutoff of > 55 µg/g with an AUC of 0.918 (92% sensitivity, 95% specificity) for predicting esophageal varices, with levels rising further in higher (Paquet grade III–IV) subgroups [1]. This provides strong proof-of-concept but leaves room for confirmation in independent cohorts with different sample sizes and patient characteristics.

The present study builds on this evidence base by evaluating fecal calprotectin in a three-group Egyptian cohort of HCV-related cirrhosis patients with esophageal varices, HCV-related cirrhosis patients without esophageal varices, and healthy controls. The aim is to determine (i) whether fecal calprotectin differs across these groups and correlates with variceal grade (modified Paquet classification), and (ii) the diagnostic performance of fecal calprotectin, including candidate cutoff values, for predicting the presence and severity of esophageal varices as a non-invasive complement to endoscopic screening.

## Methods

# Study Design and Setting

This case-control study was conducted in the Hepatology, Gastroenterology and Infectious Diseases Department, the Internal Medicine Department, and the Clinical Pathology Department, Zagazig University, over the period from October 2025 to July 2026.

## Study Population

A total of 111 participants were enrolled and allocated into three equal groups (n = 37 each):

- Group I: HCV-related cirrhotic patients with esophageal varices. This group was further subdivided according to the degree of esophageal varices, graded using the modified Paquet classification (Grade I, II, or III).
- Group II: HCV-related cirrhotic patients without esophageal varices.
- Group III: Age- and sex-matched, apparently healthy volunteers as the control group.

Diagnosis of HCV-related liver cirrhosis (Groups I and II) was based on a combination of clinical assessment, laboratory findings (including thrombocytopenia, hypoalbuminemia, and prolonged INR/PT), and imaging findings on abdominal ultrasound (coarse hepatic echotexture, nodular hepatic surface, and splenomegaly), confirmed by triphasic CT of the abdomen.

## Inclusion criteria:

- Adults aged ≥ 18 years, of both sexes, willing to provide written informed consent.
- Groups I and II: HCV-related cirrhotic patients, with HCV infection confirmed by positive HCV antibody and positive HCV RNA (PCR).
- Group III: Age- and sex-matched, apparently healthy volunteers with no history of liver disease, negative HCV antibody, and normal liver function tests and abdominal ultrasound.

Exclusion criteria: Inflammatory bowel disease, radiation proctitis, hematologic disease, malignancy (including hepatocellular carcinoma), recent surgical intervention of the small or large intestine within the preceding months, infectious diarrhea (bacterial, viral, or parasitic), a history of prolonged antibiotic use, non-steroidal anti-inflammatory drug abuse within the last 6 months, diabetes mellitus, known chronic kidney disease or congestive heart failure, hepatic encephalopathy or spontaneous bacterial peritonitis, other causes of cirrhosis (e.g., hepatitis B virus, hemochromatosis, alcoholic cirrhosis), prior endoscopic or pharmacological treatment of esophageal varices (e.g., band ligation, sclerotherapy, or beta-blocker prophylaxis), active upper gastrointestinal bleeding at the time of sampling, and pregnancy.

## Ethical Considerations

Approval was obtained from the Institutional Review Board (IRB) of Zagazig University (ZU-IRB #1550, dated 14 October 2025) prior to enrollment. Written informed consent was obtained from all participants.

## Sample Size

Sample size was calculated using OpenEpi, based on the mean ± SD of fecal calprotectin reported in controls versus patients with esophageal varices (48.4 ± 27.98 vs. 66.4 ± 33.3 µg/g; Header et al., 2022 [1]), at 95% confidence and 80% power. This yielded a total sample size of 111 participants (37 per group).

# Clinical and Laboratory Assessment

# All participants underwent the following:

- Full clinical assessment: detailed history-taking and thorough clinical examination.

- Laboratory investigations: complete blood count (including platelet count), liver function tests (ALT, AST, total bilirubin, serum albumin), blood urea nitrogen, serum creatinine, prothrombin time and international normalized ratio (INR), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), hepatitis B surface antigen (HBsAg), HCV antibody, and HCV RNA by PCR (for confirmation of active HCV infection in Groups I and II).
- Ascitic fluid analysis, where clinically indicated (i.e., in patients with clinical or radiological evidence of ascites).
- Imaging assessment: chest X-ray and pelvi-abdominal ultrasound for all participants; triphasic CT of the abdomen for Groups I and II, to confirm the diagnosis of liver cirrhosis.

Fecal calprotectin measurement and upper gastrointestinal endoscopy with variceal grading, both central to this study, are described separately below.

## Fecal Calprotectin Measurement

Stool samples were collected from all participants and stored at -20°C until analysis. Fecal calprotectin was measured by enzyme-linked immunosorbent assay (ELISA) using the Human Calprotectin L1/S100-A8/A9 Complex ELISA Kit (Catalog No. EH62RB, Invitrogen, Thermo Fisher Scientific), according to the manufacturer's instructions. A cutoff of 50 µg/g was used for correlating study results with those of existing tests.

# Upper Gastrointestinal Endoscopy and Variceal Grading

All patients in Groups I and II underwent upper gastrointestinal endoscopy. Esophageal varices, when present, were graded according to the modified Paquet classification as follows: Grade I, varices extending just above the mucosal level; Grade II, varices projecting by up to one-third of the esophageal luminal diameter, non-compressible on air insufflation; and Grade III, varices projecting more than one-third of the luminal diameter and in contact with each other.

# Statistical Analysis

Continuous variables were tested for normality (Shapiro–Wilk) and homogeneity of variance (Levene's test) within each group; most variables violated at least one assumption. For consistency and ease of clinical interpretation, all continuous variables are reported descriptively as mean ± standard deviation (SD), with the full range (minimum–maximum) shown in parentheses. Because the normality/homogeneity assumptions required for one-way ANOVA were not met, group comparisons were nonetheless performed using the non-parametric Kruskal–Wallis test, with pairwise Mann–Whitney U post-hoc comparisons and Bonferroni correction where the omnibus test was significant. Categorical variables (sex) were compared using the chi-square test. The relationship between fecal calprotectin and variceal grade was assessed using Spearman's rank correlation; Pearson correlation was additionally used to examine relationships between fecal calprotectin and other continuous clinical/biochemical

parameters, both pooled across groups and within each group separately. The diagnostic performance of fecal calprotectin for predicting the presence and grade of esophageal varices was evaluated using receiver operating characteristic (ROC) curve analysis, with area under the curve (AUC), 95% confidence intervals (bootstrap), sensitivity, specificity, positive and negative predictive values, and accuracy reported at clinically relevant cutoffs. A two-tailed p-value < 0.05 was considered statistically significant. Statistical analyses were performed using Python 3 (SciPy and scikit-learn libraries). An artificial intelligence large language model (Claude, Anthropic) was used to assist with drafting and language editing of the manuscript text; the authors reviewed, verified, and take full responsibility for all content.

## Results

# Baseline Demographic and Clinical Characteristics

Table 1
Demographic and clinical characteristics of the three study groups (mean ± SD, with range in parentheses). *Kruskal–Wallis test across the three groups; †Chi-square test.

| Variable | Group I (Cirrhosis + EV) n = 37 | Group II (Cirrhosis, no EV) n = 37 | Group III (Control) n = 37 | p-value* |
|---|---|---|---|---|
| Age (years), mean ± SD (range) | 57.0 ± 4.4 (49–64) | 56.8 ± 5.3 (45–66) | 52.7 ± 4.8 (45–60) | **0.001** |
| Male, n (%) | 19 (51.4) | 17 (45.9) | 19 (51.4) | 0.866† |
| Female, n (%) | 18 (48.6) | 20 (54.1) | 18 (48.6) | |
| Platelet count (×10³/μL), mean ± SD (range) | 78.4 ± 17.7 (45–114) | 141.4 ± 24.6 (102–193) | 298.0 ± 77.7 (170–435) | **< 0.001** |
| ALT (U/L), mean ± SD (range) | 49.0 ± 9.2 (33–67) | 55.7 ± 8.1 (46–78) | 21.1 ± 7.7 (8–35) | **< 0.001** |
| AST (U/L), mean ± SD (range) | 67.5 ± 12.9 (41–97) | 68.1 ± 9.6 (51–89) | 22.7 ± 7.3 (6–38) | **< 0.001** |
| Total bilirubin (mg/dL), mean ± SD (range) | 6.8 ± 4.4 (3.2–23.0) | 1.7 ± 0.6 (1.1–3.4) | 0.5 ± 0.3 (0.1–1.1) | **< 0.001** |
| Serum albumin (g/dL), mean ± SD (range) | 2.6 ± 0.4 (1.8–3.2) | 3.6 ± 0.3 (3.1–4.2) | 4.5 ± 0.5 (3.6–5.3) | **< 0.001** |
| INR, mean ± SD (range) | 1.7 ± 0.3 (1.5–2.7) | 1.2 ± 0.1 (1.1–1.5) | 1.0 ± 0.1 (0.8–1.2) | **< 0.001** |
| Serum creatinine (mg/dL), mean ± SD (range) | 1.4 ± 0.6 (0.5–3.4) | 0.9 ± 0.3 (0.5–1.3) | 0.7 ± 0.2 (0.5–1.1) | **< 0.001** |
| Fecal calprotectin (μg/g), mean ± SD (range) | 127.0 ± 60.6 (38–243) | 33.7 ± 13.4 (16–73) | 28.6 ± 9.1 (16–49) | **< 0.001** |

Post-hoc pairwise comparisons showed no significant difference between Group I and Group II for age ($p = 1.00$) or AST ($p = 1.00$), consistent with both groups representing cirrhotic patients of comparable disease duration. Group III (controls) differed significantly from both cirrhotic groups on nearly all clinical and biochemical parameters, confirming the biological validity of the three-group classification. Sex distribution was balanced across groups ($\chi^2 = 0.29$, $p = 0.866$), ruling out sex as a confounding variable. Age differed significantly across groups ($p = 0.001$) and is addressed as a limitation in the Discussion.

# Fecal Calprotectin Across Study Groups

Fecal calprotectin differed significantly across the three groups (Kruskal–Wallis $H = 66.22$, $p < 0.001$). Mean fecal calprotectin was markedly higher in Group I [127.0 ± 60.6 µg/g (range 38–243)] compared with Group II [33.7 ± 13.4 µg/g (range 16–73)] and Group III [28.6 ± 9.1 µg/g (range 16–49)].

# Pairwise post-hoc comparisons (Bonferroni-corrected):

- Group I vs Group II: $p < 0.001$ (significant)
- Group I vs Group III: $p < 0.001$ (significant)
- Group II vs Group III: $p = 0.127$ (not significant)

This pattern indicates that fecal calprotectin elevation is associated with the presence of esophageal varices, with a degree of overlap in individual values between groups (e.g., some Group I patients have calprotectin as low as 38 µg/g, within the range seen in Group II).

# [Figure 1 — submitted as separate file Fig. 1.png; see legend below]

*Figure 1. Distribution of fecal calprotectin levels across the three study groups.*

# Correlation Between Fecal Calprotectin and Variceal Grade

Within Group I, fecal calprotectin showed a moderate-to-strong, statistically significant positive correlation with variceal grade (modified Paquet classification) (Spearman's $\rho = 0.575$, $p < 0.001$). Mean calprotectin increased with variceal severity, though with wider spread and some overlap between adjacent grades:

Table 2
Fecal calprotectin by variceal grade among Group I patients (Kruskal–Wallis $H = 12.10$, $p = 0.0024$).

| Variceal Grade | n | Fecal Calprotectin, µg/g mean ± SD (range) |
|---|---|---|
| Grade I | 10 | 72.4 ± 17.2 (39–89) |
| Grade II | 18 | 133.9 ± 45.5 (38–190) |
| Grade III | 9 | 173.8 ± 77.2 (38–243) |

# [Figure 2 — submitted as separate file Fig. 2.png; see legend below]

*Figure 2. Fecal calprotectin levels rise with variceal grade, with increasing variability at higher grades.*

# Diagnostic Performance: ROC Curve Analysis

ROC curve analysis was performed using fecal calprotectin to discriminate patients with esophageal varices (Group I) from those without (Groups II + III combined, n = 74). Discrimination was very good: AUC = 0.970 (95% CI 0.941–0.992).

Table 3
Diagnostic performance of fecal calprotectin for detecting esophageal varices, AUC = 0.970 (95% CI 0.941–0.992), at two candidate cutoffs.

| Parameter | Youden-optimal cutoff (≥ 71 µg/g) | Selected cutoff (> 50 µg/g) |
|---|---|---|
| Sensitivity | 81.1% (30/37) | 81.1% (30/37) |
| Specificity | 98.6% (73/74) | 94.6% (70/74) |
| PPV | 96.8% | 88.2% |
| NPV | 91.2% | 90.9% |
| Overall accuracy | 92.8% | 90.1% |

# [Figure 3 — submitted as separate file Fig. 3.png; see legend below]

*Figure 3. ROC curve for fecal calprotectin in predicting the presence of esophageal varices (AUC = 0.970), with both candidate cutoffs marked.*

Both cutoffs give identical sensitivity (81.1%) because no additional patients fall between 50 and 71 µg/g. The Youden-optimal cutoff of ≥ 71 µg/g yields higher specificity and PPV, while > 50 µg/g remains a reasonable, easier-to-recall clinical threshold with a modest trade-off in specificity. Seven Group I patients (calprotectin 38–68 µg/g) were missed by both cutoffs (false negatives).

AUC for predicting high-grade (Grade II–III) versus low-grade (Grade I) varices within Group I was 0.837 (95% CI 0.692–0.962); at a cutoff of ≥ 112 µg/g, sensitivity was 81.5% (22/27) and specificity was 100% (10/10, PPV 100%, NPV 66.7%). This subgroup analysis is limited by small sample size (only 9 Grade III patients).

# [Figure 4 — submitted as separate file Fig. 4.png; see legend below]

*Figure 4. ROC curve for fecal calprotectin in distinguishing high-grade from low-grade varices (AUC = 0.837).*

# Correlation of Fecal Calprotectin with Other Clinical Parameters

A pooled Pearson correlation matrix (n = 111, all groups combined) showed fecal calprotectin significantly correlated with every parameter tested, most strongly with INR (r = 0.688), serum albumin (r = -0.685), and total bilirubin (r = 0.596) (all p < 0.001).

Table 4

*Pearson correlation coefficients between fecal calprotectin and clinical/biochemical parameters, whole cohort (n = 111).* When the same correlations were recalculated separately within each group (holding group membership constant), almost none remained significant:

| Parameter | Pearson's r (vs. Calprotectin) | p-value |
|---|---|---|
| Age | 0.263 | 0.005 |
| Platelet count | -0.526 | < 0.001 |
| ALT | 0.268 | 0.005 |
| AST | 0.377 | < 0.001 |
| Total bilirubin | 0.596 | < 0.001 |
| Serum albumin | -0.685 | < 0.001 |
| INR | 0.688 | < 0.001 |
| Serum creatinine | 0.498 | < 0.001 |

Table 5

Pearson correlation coefficients between fecal calprotectin and each parameter, calculated separately within each group (n = 37 per group).

| Parameter | Group I r (p-value) | Group II r (p-value) | Group III r (p-value) |
|---|---|---|---|
| Age | 0.314 (0.058) | 0.050 (0.768) | -0.068 (0.689) |
| Platelet count | 0.011 (0.949) | -0.038 (0.825) | -0.079 (0.643) |
| ALT | 0.111 (0.513) | -0.218 (0.195) | -0.108 (0.524) |
| AST | 0.080 (0.638) | -0.274 (0.101) | -0.215 (0.201) |
| Total bilirubin | 0.080 (0.637) | -0.130 (0.443) | -0.332 (0.045) |
| Serum albumin | -0.392 (0.017) | -0.031 (0.856) | 0.084 (0.621) |
| INR | 0.219 (0.193) | 0.043 (0.799) | -0.252 (0.132) |
| Serum creatinine | 0.096 (0.573) | 0.213 (0.205) | -0.207 (0.219) |

Only two associations reached significance within a single group — serum albumin within Group I (r = -0.392, p = 0.017) and total bilirubin within Group III (r = -0.332, p = 0.045, likely a chance finding given multiple comparisons and the borderline p-value). This indicates that the large pooled correlations in Table 4 reflect the disease spectrum across groups (healthy → cirrhosis → cirrhosis with varices) rather than a direct biological relationship between calprotectin and routine liver-function or renal markers.

## Discussion

This case-control study evaluated fecal calprotectin as a non-invasive marker of esophageal varices in 111 participants with HCV-related liver cirrhosis and healthy controls. The following sections discuss our findings in the order presented in the Results, comparing each with relevant published literature.

# Baseline Demographic and Clinical Characteristics

Age differed significantly across the three groups (p = 0.001), with controls somewhat younger than the two cirrhotic groups, while sex distribution was balanced (p = 0.866). Some prior calprotectin-in-cirrhosis studies specifically age- and sex-matched their control group to avoid this imbalance [7, 8], and this is worth noting as a limitation of our design (discussed further below) rather than an unusual finding. The expected gradient of worsening platelet count, liver function tests, and coagulation profile from Group III through Group II to Group I mirrors the pattern consistently reported in comparable cirrhosis cohorts and supports the biological validity of our three-group classification [1, 3].

# Fecal Calprotectin Across Study Groups

Fecal calprotectin was significantly higher in Group I (cirrhosis with esophageal varices) than in Group II (cirrhosis without varices) or Group III (controls), with no significant difference between Groups II and III. This pattern — elevation specifically tied to the presence of varices rather than to cirrhosis in general — parallels the design and conclusion of Header et al. (2022), the most directly comparable prior study, which similarly found significantly higher fecal calprotectin in Egyptian HCV-cirrhotic patients with esophageal varices than in those without varices or in healthy controls [1]. More broadly, our finding that cirrhotic patients have higher fecal calprotectin than healthy controls is consistent with several independent cohorts: Alempijević et al. reported a mean fecal calprotectin of 189.1 ± 168.0 µg/g in 60 cirrhotic patients versus 35.0 ± 26.0 µg/g in 37 healthy controls (p < 0.001) [7], and Gundling et al. similarly found significantly higher fecal calprotectin concentrations in 61 cirrhotics compared with controls (p < 0.001) [8]. Our Group I mean (127.0 ± 60.6 µg/g) and Group III mean (28.6 ± 9.1 µg/g) fall within a broadly comparable range to these reports, notwithstanding differences in patient populations, cirrhosis etiology (only Alempijević and Gundling included non-HCV etiologies), and assay kits used across studies.

# Correlation Between Fecal Calprotectin and Variceal Grade

Fecal calprotectin correlated positively with variceal grade in our cohort (Spearman's ρ = 0.575, p < 0.001), consistent with Header et al.'s report of a graded increase in fecal calprotectin with more

advanced (Paquet grade III–IV) varices [1]. This correlation coefficient is also strikingly similar in magnitude to that reported by Gundling et al. between fecal calprotectin and Child-Pugh score in a general cirrhosis population (ρ = 0.577, p < 0.001) [8], suggesting fecal calprotectin tracks portal-hypertension-related disease severity to a comparable degree whether that severity is expressed through the Child-Pugh score or, as in our study, through variceal grade specifically. Not all prior work agrees on this point, however: Alempijević et al. found no significant difference in fecal calprotectin across Child-Pugh classes or MELD scores in their cohort, although they did find a significant association with hepatic encephalopathy grade [7]. Taken together with our own within-group correlation analysis (see below), this discrepancy across studies suggests that fecal calprotectin's relationship with liver disease severity markers may be inconsistent or population-dependent, whereas its relationship with portal-hypertension-specific endpoints — esophageal varices and their grade in our study, hepatic encephalopathy and spontaneous bacterial peritonitis in others [7, 8, 4] — appears more reproducible across cohorts.

# Diagnostic Performance: ROC Curve Analysis

Fecal calprotectin discriminated patients with versus without esophageal varices with an AUC of 0.970 (95% CI 0.941–0.992), which is numerically higher than, but broadly consistent with, the AUC of 0.918 (cutoff > 55 µg/g; 92% sensitivity, 95% specificity) reported by Header et al. for the same clinical question in a larger Egyptian HCV-cirrhosis cohort [1]. Our cutoffs (≥ 71 µg/g Youden-optimal, or the pre-specified > 50 µg/g) achieved a different balance of sensitivity and specificity (81.1% sensitivity at 94.6–98.6% specificity) than Header et al.'s reported operating point, which may reflect differences in sample size, Grade III subgroup size, or population-specific variability rather than a genuine conflict between studies, since both converge on fecal calprotectin being a strong discriminator overall. Compared with other non-invasive tools for predicting esophageal varices — platelet count, spleen diameter, the platelet/spleen-diameter ratio, and composite scores such as APRI, FIB-4, and the platelet–albumin–bilirubin (PALBI) score, which have generally reported AUCs in the 0.7–0.85 range [2, 3] — the diagnostic performance of fecal calprotectin observed here and in Header et al. [1] compares favorably, supporting its candidacy as a non-invasive triage tool. Diagnostic cutoffs reported for fecal calprotectin in other cirrhosis-related complications are considerably higher than ours — for example, cutoffs around 164–292 µg/g have been proposed for hepatic encephalopathy or spontaneous bacterial peritonitis [8, 4] — underscoring that fecal calprotectin thresholds are outcome-specific and should not be extrapolated across different clinical questions.

# Correlation of Fecal Calprotectin with Other Clinical Parameters

When fecal calprotectin was correlated with routine liver-function and renal parameters across the whole cohort (pooled Pearson correlation, n = 111), strong associations emerged for nearly every parameter (e.g., INR, r = 0.688; albumin, r = -0.685) — a pattern broadly consistent with Gundling et al.'s report of fecal calprotectin correlating with Child-Pugh and MELD scores in a pooled cirrhosis population [8]. However, when we recalculated these correlations separately within each of our three groups, almost none remained significant, with the exception of serum albumin within Group I (r = -0.392, p = 0.017) and,

more marginally, total bilirubin within Group III (r = -0.332, p = 0.045); given the number of correlations tested and the borderline p-value, the latter is more plausibly a chance finding than a genuine effect, and neither materially changes the overall picture. This indicates that the strong pooled correlations were driven largely by group membership — i.e., the fact that the three groups differ systematically on nearly every parameter — rather than by a direct, generalizable biological relationship between fecal calprotectin and routine hepatic or renal function. This finding helps reconcile the discrepancy noted above between studies that did [8] and did not [7] find a relationship between fecal calprotectin and conventional severity scores: pooled analyses across heterogeneous groups may be prone to overstating such relationships, and within-group analysis — rarely reported in the existing calprotectin literature — offers a more conservative and specific estimate. Mechanistically, our results are consistent with the proposed gut–liver axis pathway, whereby portal hypertension promotes intestinal mucosal congestion, increased permeability, and bacterial translocation, upregulating neutrophil-driven fecal calprotectin release largely in proportion to portal-hypertension-related complications (varices in our study) rather than general hepatocellular dysfunction [4, 5].

## Strengths and Limitations

This study has several strengths, including a well-defined three-group design that allowed the variceal-specific signal of fecal calprotectin to be distinguished from its association with cirrhosis in general (evidenced by the lack of difference between Groups II and III), a standardized and widely used grading system (modified Paquet classification) for variceal severity, and — building on the existing literature — the use of both pooled and within-group correlation analyses to guard against confounding by group membership, an approach not commonly reported in prior calprotectin-in-cirrhosis studies.

Several limitations should also be acknowledged. First, this was a single-center, case-control study with a comparatively modest sample size (37 per group), particularly limiting the high-grade varices subgroup analysis (only 9 Grade III patients); the reported confidence interval for this secondary ROC analysis was correspondingly wide (AUC 95% CI 0.692–0.962). Second, age differed significantly between groups (p = 0.001); although fecal calprotectin was not correlated with age within any single group, residual confounding by age or other unmeasured factors cannot be entirely excluded, and future studies would benefit from formal age-matching as used in some prior calprotectin studies [7, 8]. Third, the case-control design, with retrospective grouping by endoscopic findings, precludes conclusions about causality or the temporal evolution of fecal calprotectin as varices develop or progress. Fourth, this study did not directly compare fecal calprotectin against other non-invasive scores (e.g., APRI, FIB-4, PALBI) within the same cohort, so relative — rather than only literature-based — comparisons of diagnostic performance could not be made. Finally, as with any biomarker showing very high discriminative performance in a single cohort, external validation in an independent, larger, and ideally multi-center population is recommended before the proposed cutoffs are adopted in clinical practice.

## Conclusion

Fecal calprotectin is significantly elevated in patients with HCV-related liver cirrhosis and esophageal varices compared with cirrhotic patients without varices and healthy controls, and rises progressively with variceal grade. It discriminates the presence of esophageal varices with high accuracy (AUC = 0.970) and shows good, though imperfect, performance in distinguishing high-grade from low-grade varices. Because seven patients with confirmed varices had comparatively low fecal calprotectin, it should not be used to rule out varices with certainty; rather, fecal calprotectin is best positioned as a simple, low-cost, non-invasive triage tool to help prioritize patients for endoscopic screening — particularly valuable in resource-limited settings — alongside, rather than in place of, upper gastrointestinal endoscopy. Larger, prospective, multi-center studies are recommended to validate the proposed cutoffs (≥ 71 μg/g and > 50 μg/g) and to evaluate fecal calprotectin in combination with existing non-invasive scores (e.g., APRI, FIB-4, PALBI) before clinical adoption.

## Abbreviations

AUC
area under the curve
CI
confidence interval
CRP
C-reactive protein
ELISA
enzyme-linked immunosorbent assay
ESR
erythrocyte sedimentation rate
HBsAg
hepatitis B surface antigen
HCV
hepatitis C virus
INR
international normalized ratio
IRB
Institutional Review Board
MELD
Model for End-Stage Liver Disease
NPV
negative predictive value
PALBI
platelet–albumin–bilirubin score
PCR
polymerase chain reaction

PPV
positive predictive value
PT
prothrombin time
ROC
receiver operating characteristic
SD
standard deviation.

# Declarations

### Ethics approval and consent to participate

This study was approved by the Institutional Review Board (IRB) of Zagazig University (ZU-IRB #1550, dated 14 October 2025). Written informed consent to participate was obtained from all participants prior to enrollment.

### Consent for publication

Not applicable.

### Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

### Competing interests

The authors declare that they have no competing interests.


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### Authors' contributions

All authors contributed equally to the conception, design, data collection, analysis, and writing of this manuscript, and all approved the final version for submission.


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Not applicable.


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# Figures

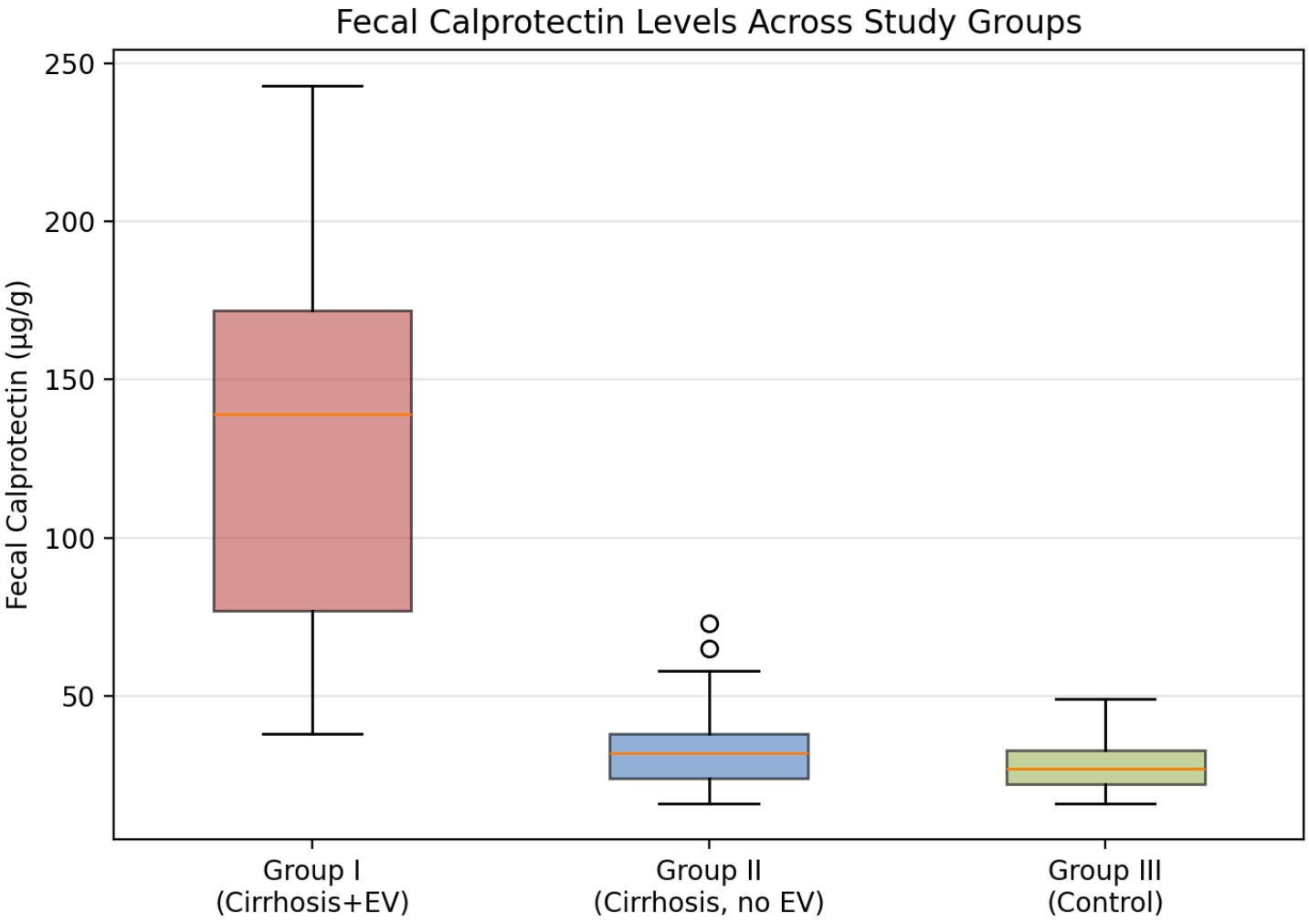



**Figure 1**

*Distribution of fecal calprotectin levels across the three study groups.*

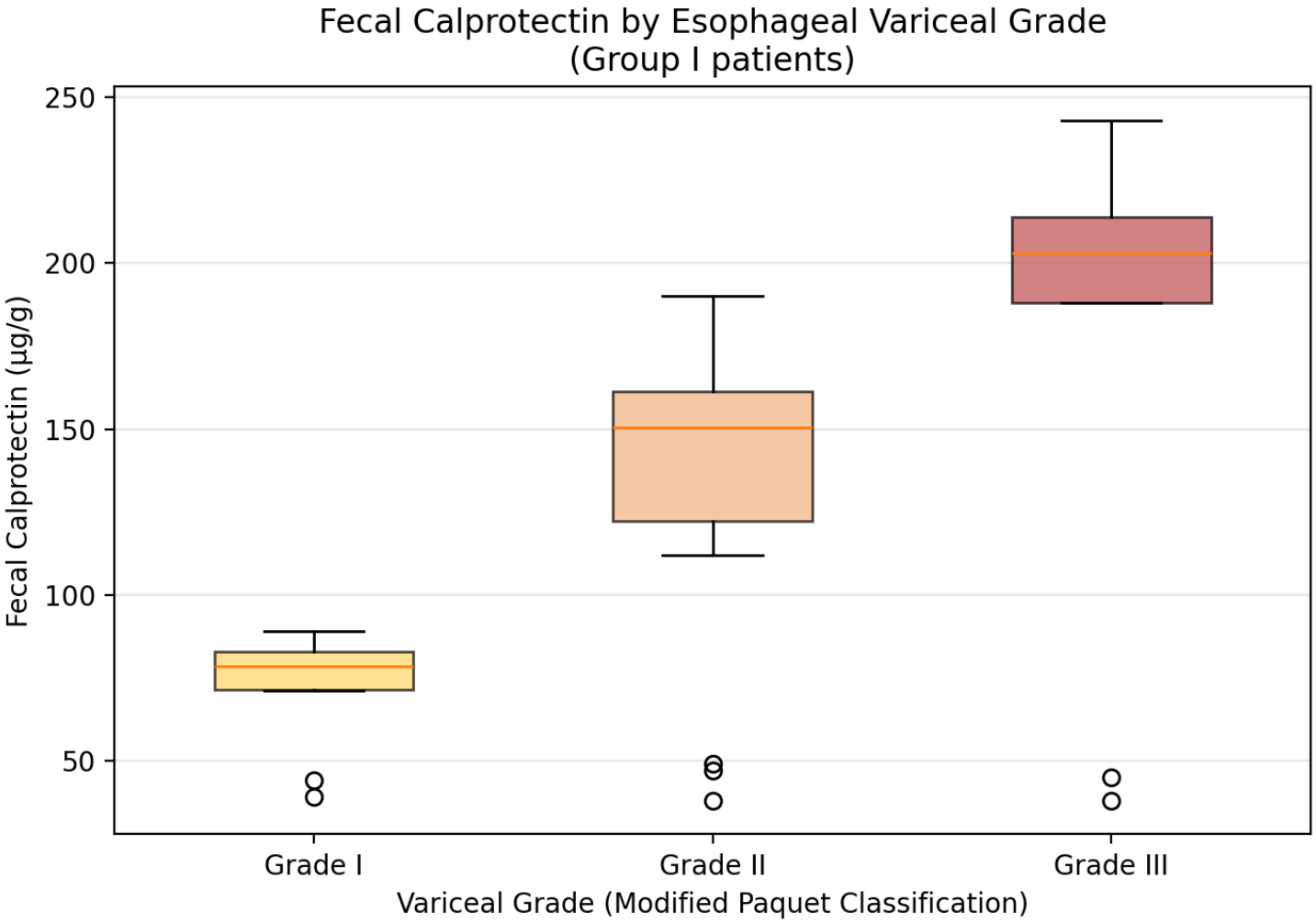



**Figure 2**

*Fecal calprotectin levels rise with variceal grade, with increasing variability at higher grades.*

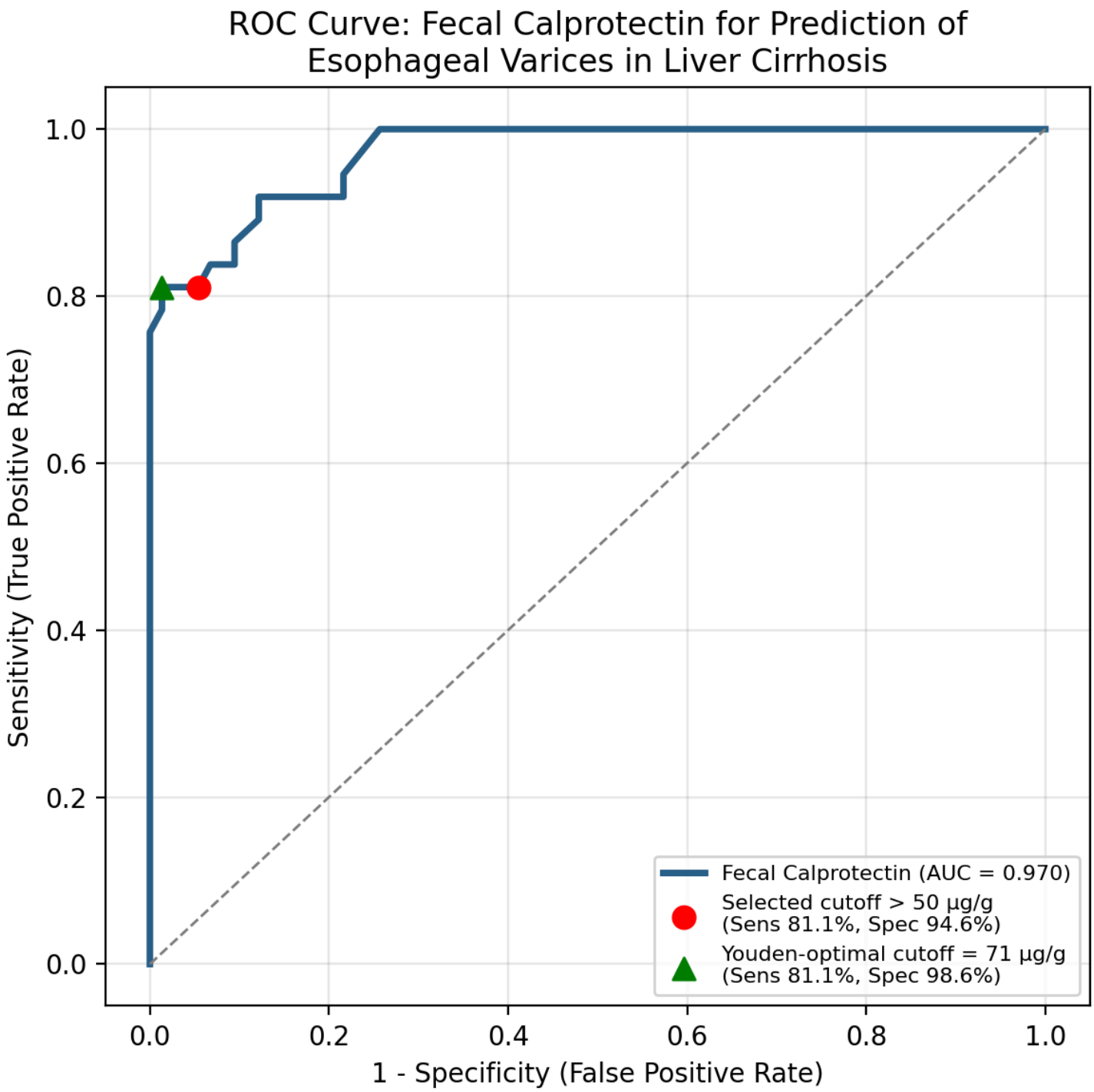



**Figure 3**

*ROC curve for fecal calprotectin in predicting the presence of esophageal varices (AUC = 0.970), with both candidate cutoffs marked.*

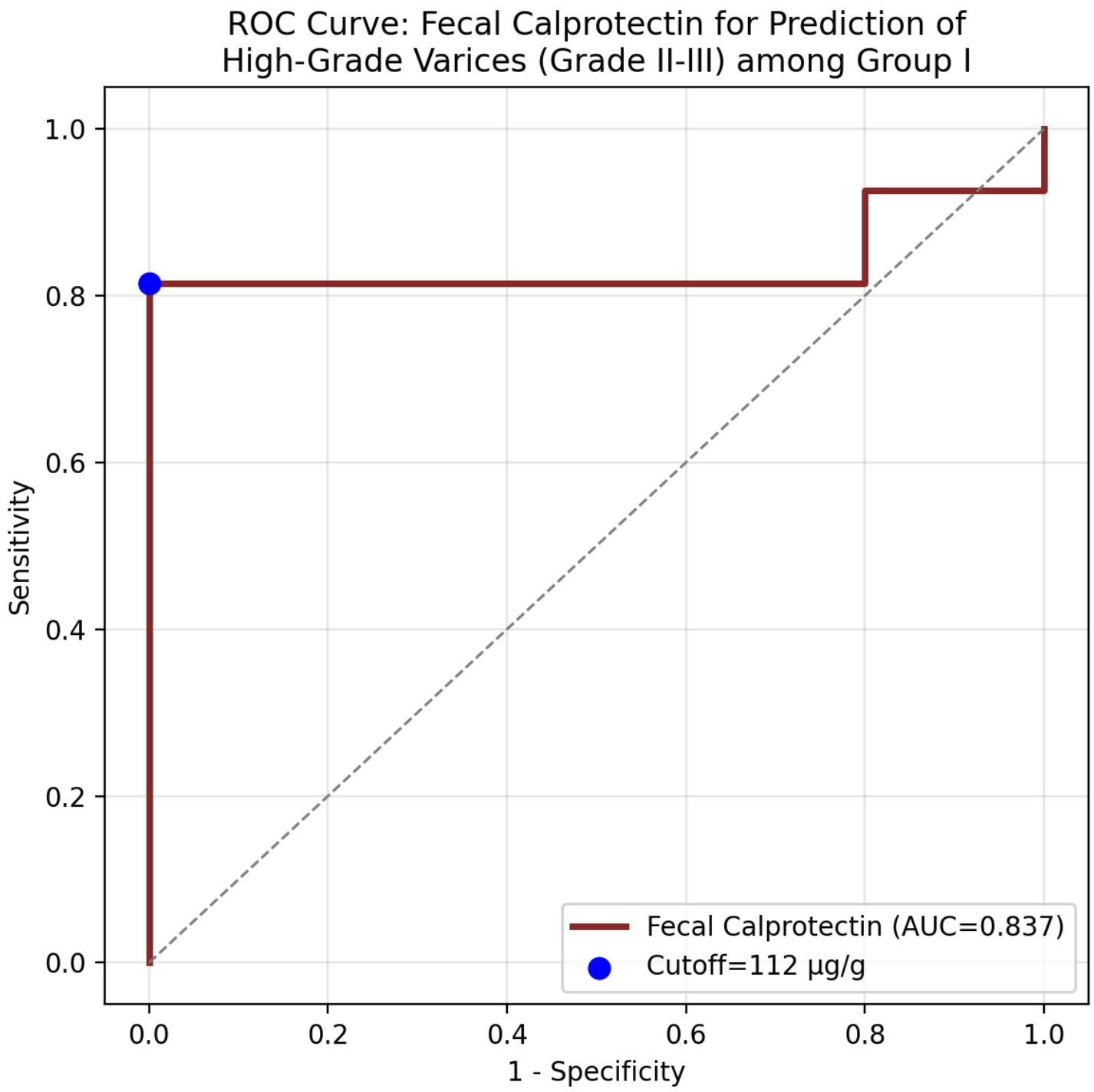



**Figure 4**

*ROC curve for fecal calprotectin in distinguishing high-grade from low-grade varices (AUC = 0.837*