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Research Article

# Fecal Calprotectin in Nosocomial Diarrhea: A Prospective Observational Study

**Jaroonsakchai W[1], Limsrivilai J[1,2*], Phaophu P[1], Subdee N[1], Ngamskulrungroj P[3], Pausawasdi N[1,2], Charatcharoenwitthaya P[1,2], Pongprasobchai S[1,2] and Leelakusolvong S[1,2]**

[1]Division of Gastroenterology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

[2]Siriraj GI Endoscopy center, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand

[3]Department of Microbiology, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand

**Abbreviations:** AAD: antibiotic-associated diarrhea; CDI: Clostridium difficile infection; GI: gastrointestinal; IQR: interquartile range; LR: likelihood ratio; NPV: negative predictive value; PPV: positive predictive value; ROC: receiver operating characteristic; WBC: white blood cell

**Keywords:** Nosocomial diarrhea; fecal calprotectin; Clostridium difficile

## 1. Abstract

**1.1. Background:** Fecal calprotectin (FC) has an essential role in differentiating inflammatory diarrhea from functional diarrhea in an outpatient setting; however, its role in nosocomial diarrhea remains not well explored.

**1.2. Methods:** This is a prospective observational study. We included adult inpatients with nosocomial diarrhea and categorized them into diarrhea likely (group A) and unlikely (group B) to have lesions in the colonic mucosa. Group A included infectious diarrhea such as Clostridium difficile and ischemic colitis. Group B comprised tube-feeding diarrhea, non-C. difficile antibiotic-associated diarrhea, and drug-induced diarrhea. The FC levels were compared between the two groups.

**1.3. Results:** 135 patients were included, 45 in group A and 90 in group B. Median FC was 902 mg/kg (interquartile range [IQR] 549-2,175) of feces in group A, significantly higher than the median level of 377 mg/kg (IQR 141-664) of feces in group B ($p<0.001$). The area under the receiver operating characteristic curve was 0.798 (95% confidence interval: 0.717-0.879). At the standard cutoff of 50 mg/kg of feces, the sensitivity and specificity were 97.8% and 7.8%, respectively.

**1.4. Conclusions:** FC was significantly higher in nosocomial diarrhea likely to have mucosal lesions; however, its clinical usefulness was limited due to poor specificity.

**1.5. Trial registration:** The trial was registered at ClinicalTrials.gov. (reg. no. NCT04491799. Registered on 26/04/2020).

## 2. Introduction

Nosocomial diarrhea is defined as diarrhea that develops after 72 hours of hospitalization [1]. It is a commonly occurring condition with a reported prevalence of 14-21% in patients in the intensive care unit [2]. Common causes of nosocomial diarrhea can be grouped into two main groups according to the mucosal abnormality [3]. The first group includes conditions with gastrointestinal (GI) mucosal lesions, which mainly comprises gastrointestinal infections, including Clostridium difficile infection (CDI) and other infections such as cytomegalovirus infection, and some other conditions such as ischemic colitis. The second group includes conditions with normal colonic mucosa, including antibiotic-associated diarrhea (AAD) without CDI, tube-feeding-associated diarrhea, and drug-induced diarrhea [2, 3]. The current management recommendations include ruling out infections, particularly C. difficile infection, which is found in a majority of cases. Afterward, diet modification and

***Correspondence to**: Julajak Limsrivilai, Division of Gastroenterology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, 2 Wanglang Road, Bangkoknoi, Bangkok 10700, Thailand, Tel: (+66) 2-419-7281; Fax: (+66) 2-411-5013; E-mail: julajak.lim@mahidol.ac.th

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supportive treatment with anti-diarrheal agents are recommended [4]. However, some patients have ongoing diarrhea despite receiving appropriate management, which could be due to undetected C. difficile, unresolved tube-feeding diarrhea/AAD, or other causes such as reactivation of cytomegalovirus infection and ischemic enterocolitis. Colonoscopy may be required in this setting to establish a definite diagnosis. Nonetheless, colonoscopy is invasive and has some complications, particularly in patients with a critical illness. Therefore, selecting patients who are likely to have mucosal lesions and gain benefit from colonoscopy is warranted. A test to differentiate diarrhea with and without mucosal lesions should be helpful in this situation. Unfortunately, a conventional test like stool white blood cell (WBC) has a low sensitivity in detecting mucosal lesions in an inpatient setting [3].

Fecal calprotectin is an easy, non-invasive test that can differentiate inflammatory bowel disease and other functional disorders in an outpatient setting [5]. However, the data in an inpatient setting is limited to the studies focusing on diagnosis and assessment of the severity of C. difficile-associated colitis [6-11]. Our main objective was to study the performance of fecal calprotectin for distinguishing patients with nosocomial diarrhea likely to have mucosal lesions from those unlikely to have mucosal lesions.

## 3. Materials and Methods

### 3.1. Study Design

This study is a prospective observational study conducted from February 2019 to May 2020. The protocol was approved by Siriraj Institutional Review Board, an independent ethics committee according to local requirements, and informed consent was obtained from all participants before study enrollment. The trial was registered at ClinicalTrials.gov. (reg. no. NCT04491799).

### 3.2. Participants and recruitment process

Adult patients aged at least 18 years who developed nosocomial diarrhea were eligible for inclusion. The definition of nosocomial diarrhea was a development of loose stool or watery stool (Bristol Stool Form type 6-7) at least three times per day after hospitalization for longer than 72 hours. The patients with known underlying GI inflammatory conditions such as inflammatory bowel disease were excluded. The stool samples were collected and stored at -20℃ at enrollment. Afterward, study patients were managed by treating physicians. All study patients were followed up until death or discharge from the hospital. The stool samples were tested for calprotectin at the end of the study. Therefore, treating physicians did not know the fecal calprotectin values.

Eligible patients were required to have stool microscopic examination and stool test for C. difficile infection. Colonoscopy was performed in some patients when the stool tests could not make the diagnosis, and the clinical did not improve by the conservative management, depending on the treating physician's decision.

The clinical data, investigations, final diagnoses, and clinical outcomes were prospectively collected. The definitions of each diagnosis are shown as follows:

- Clostridium difficile infection: positive stool C. difficile toxin. The test was performed on a BD MAX System detecting C. difficile toxin B gene (tcdB) by real-time polymerase chain reaction (PCR) technique.
- Presumed Clostridium difficile infection: the presence of stool WBC more than 5/high power field, but negative for C. difficile toxin with clinical response to C. difficile treatment in one week
- Cytomegalovirus infection: histopathological identification of viral inclusion body or positive immunohistochemistry
- Bacterial enterocolitis: stool culture growth of bacterial pathogen
- Strongyloides stercoralis infection: detected larvae of Strongyloides stercoralis in stool examination
- Ischemic colitis: endoscopic findings and pathological findings suggestive of colonic ischemia
- Tube-feeding-associated diarrhea: no WBC or organisms were detected in stool, and diarrhea responded to diet modification, such as decreased concentration or rate, or changed the type of enteral diet
- Antibiotic-associated diarrhea (AAD): no WBC or organisms were detected in stool, and diarrhea responded to stopping or changing antibiotics with or without cholestyramine
- Drug-induced diarrhea: no WBC or organisms were detected in stool. Diarrhea occurred within 48 hours after taking potential drugs, such as elixir KCL or laxative agents, and responded to discontinuation of those medications.

Treatment response was defined as a reduction in the frequency of bowel movements to less than three times per day. If a definite diagnosis could not be made, those patients were excluded from the study.

Study participants were divided into the group likely to have mucosal lesions (group A) and those likely to have normal colonic mucosa (group B). Group A included patients with diarrhea associated with gastrointestinal infections, including C. difficile, other bacteria, cytomegalovirus, strongyloidiasis, and other conditions, such as ischemic colitis. Group B included the patients with tube-feeding diarrhea, AAD, and drug-induced diarrhea.

### 3.3. Fecal calprotectin measurement

The stool samples were extracted at room temperature using an EliA Stool Extraction Kit. Fecal calprotectin levels were measured by EliA Calprotectin Test Kit on a Phadia 100 analyzer based on the principle of a two-site sandwich fluoroenzyme immunoassay. The results were reported in mg/kg of feces with a measurement range of 15 to ≥3,000 mg/kg of feces. A fecal calprotectin level higher than 3,000 mg/kg of feces was defaulted to 3,000 mg/kg for analysis in this study.

### 3.4. Study outcomes

The primary outcome was the fecal calprotectin performance in distinguishing nosocomial diarrhea likely to have mucosal lesions from those unlikely to have mucosal lesions.

### 3.5. Statistical analysis

The continuous data are presented as mean and standard deviation if normally distributed and as median and range or interquartile range (IQR) if not normally distributed. Categorical variables are presented as frequency and percentage. Comparison of factors and patient characteristics between group A and group B were undertaken using an independent t-test or Wilcoxon rank-sum test for continuous variables and using the chi-square test or Fisher's exact test for categorical variables. The best fecal calprotectin level cutoff for distinguishing between groups A and B was determined using receiver operating characteristic (ROC) curve analysis. The performance of different cutoff values in the diagnosis of diarrhea likely to have mucosal lesions was determined using the following parameters: sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and positive and negative likelihood ratio (LR). A p-value < 0.05 was considered statistically significant. The statistical analyses were performed using SAS Statistics software (SAS, Inc., Cary, North Carolina, USA) and R program version 4.0.1(R Foundation for Statistical Computing, Vienna, Austria). The OptimalCutpoints[12] software packages were used.

## 4. Results

### 4.1. Baseline characteristics

One hundred and forty-two patients were assessed. Seven were excluded because a definite diagnosis could not be established. The remaining 135 patients were analyzed in this study.

Baseline characteristics are shown in Table 1. The mean age was 74 years, and 41% were male. About 80% of patients had comorbid illnesses, such as atherosclerotic diseases, chronic kidney diseases, chronic liver diseases, autoimmune diseases, and malignancies. The most common indication for hospitalization was a severe infection.

At the time of stool collection, 46% were on a mechanical ventilator, 36% required inotropic agents, and 8% needed acute hemodialysis. Seventy-six percent of patients required tube-feeding enteral nutrition with a median rate of 600 cc/hour (range: 10-600). Ninety-eight percent of subjects were receiving antibiotics with a median duration of 4.5 days (range:0-26) before diarrhea developed.

Diarrhea developed at a median duration of 7 days of hospitalization. Four (3.0%) and 14 (10.4%) patients had bloody and mucous diarrhea, respectively. The mean maximum number of bowel movements per day and volume of stool per day were 6.4 times and 732 ml, respectively. Abdominal pain, fever, and feeding intolerance were found in 8.9%, 60.7%, and 9.6%, respectively. The mean hemoglobin and albumin levels were 9.50 g/dL and 2.66 g/dL, respectively.

The definite diagnoses of study patients are shown in Table 2. Forty-five patients (33.3%) were in group A; the diagnoses included CDI, GI-CMV disease, bacterial enterocolitis, Strongyloides stercoralis, and ischemic colitis. Ninety patients (66.7%) were in group B.

The patients in group A were significantly younger. Passing bloody and mucous stools, abdominal pain, and feeding intolerance was found more in group A while tube-feeding nutrition was required more in group B. Stool WBC was found in only 11 (24.4%) patients in group A. Other parameters were not statistically different between groups Table 1 and 2.

**Table 1:** Clinical and laboratory parameters of total cohort and comparison between diarrhea likely to have mucosal lesions (Group A) and unlikely to have mucosal lesions (Group B).

| | Total cohort (n=135) | Group A (n=45) | Group B (n=90) | *p*-value |
|---|---|---|---|---|
| Demographic data | | | | |
| Age | 74.2 ± 14.0 | 69.3 ± 16.1 | 76.6 ± 12.3 | 0.01 |
| Male | 55 (40.7%) | 21 (46.7%) | 34 (37.8%) | 0.322 |
| Significant comorbid illness | 109 (80.7%) | 39 (86.7%) | 70 (77.8%) | 0.217 |
| Hospitalizations | | | | |
| Indication for hospitalization | | | | 0.126 |
| Infections | 98 (72.6%) | 28 (62.2%) | 70 (77.8%) | |
| Cancers | 7 (5.2%) | 4 (8.9%) | 3 (3.3%) | |
| Major organ diseases | 30 (22.2%) | 13 (28.9%) | 17 (18.9%) | |
| In hospital setting | | | | |
| On ventilator | 62 (45.9%) | 16 (35.6%) | 46 (51.1%) | 0.087 |
| On inotropic agents | 48 (35.6%) | 15 (33.3%) | 33 (36.7%) | 0.703 |
| Need acute hemodialysis | 11 (8.2%) | 3 (6.7%) | 8 (8.9%) | 0.751 |
| Sepsis | 61 (45.2%) | 22 (48.9%) | 39 (43.3%) | 0.541 |
| Enteral nutrition and antibiotics | | | | |
| Tube feeding enteral nutrition | 102 (75.6%) | 23 (51.1%) | 79 (87.8%) | <0.001 |
| Antibiotics | 132 (97.8%) | 43 (95.6%) | 89 (98.9%) | 0.258 |
| Duration of antibiotics (median, range) | 4.5 (0 – 26) | 4 (0 – 18) | 5 (0 – 26) | 0.382 |
| Clinical manifestations | | | | |
| Day after admission (median, range) | 7.0 (3 – 95) | 6 (3 – 95) | 7 (3 – 45) | 0.434 |
| Diarrhea character | | | | |
| Watery | 135 (100%) | 45 (100%) | 90 (100%) | |
| bloody | 4 (3.0%) | 4 (8.9%) | 0 (0.0%) | 0.011 |

| | | | | |
|---|---|---|---|---|
| mucous | 14 (10.4%) | 11 (24.4%) | 3 (3.3%) | <0.001 |
| Maximum bowel movement/day | 6.4 ± 2.3 | 6.73 ± 3.16 | 6.18 ± 1.69 | 0.284 |
| Maximum volume/day | 732 ± 423 | 696 ± 443 | 750 ± 414 | 0.525 |
| Abdominal pain | 12 (8.9%) | 8 (17.8%) | 4 (4.4%) | 0.02 |
| Fever | 82 (60.7%) | 27 (60.0%) | 55 (61.1%) | 0.9 |
| Feeding intolerance | 13 (9.6%) | 9 (20.0%) | 4 (4.4%) | 0.01 |
| Laboratory tests | | | | |
| Hemoglobin | 9.50 ± 1.64 | 9.4 ± 1.9 | 9.6 ± 1.5 | 0.59 |
| White blood cell count (per $mm^3$) | 11161 ± 5764 | 11677 ± 6462 | 10903 ± 5402 | 0.464 |
| Platelet count (per $mm^6$) | 230 ± 125 | 220 ±143 | 236 ±117 | 0.524 |
| Creatinine (median, range) | 1.13 (0.27–11.26) | 1.26 (0.32–11.18) | 1.08 (0.27 – 11.26) | 0.448 |
| Bicarbonate | 22.9 ± 4.9 | 22.0 ± 4.3 | 23.4 ± 5.1 | 0.114 |
| Albumin | 2.66 ± 0.53 | 2.66 ± 0.56 | 2.66 ± 0.52 | 0.956 |
| Presence of stool white blood cell | 11 (8.2%) | 11 (24.4%) | 0 (0%) | <0.001 |
| Outcome | | | | |
| Dead | 38 (28.2%) | 16 (35.6%) | 22 (24.4%) | 0.176 |

**Table 2:** Final diagnoses of patients in this cohort

| Definite diagnosis | |
|---|---|
| *Clostridium difficile* infection | 32 (23.7%) |
| Presumed *C.difficile* infection | 5 (3.7%) |
| Gastrointestinal cytomegalovirus disease | 3 (2.2%) |
| Bacterial enterocolitis | 2 (1.5%) |
| *Strongyloides stercoralis* | 2 (1.5%) |
| Ischemic colitis | 1 (0.7%) |
| Tube-feeding diarrhea | 41 (30.4%) |
| Drug-induced diarrhea | 15 (11.1%) |
| Antibiotic-associated diarrhea | 34 (25.2%) |

### 4.2. Fecal calprotectin in diagnosis of nosocomial diarrhea

The level of fecal calprotectin in group A was significantly higher than the level in group B, with a median level of 902 mg/kg (interquartile range [IQR]: 549-2,175) and 377 mg/kg (IQR: 141-664), respectively (p<0.001) (Figure 1A). Using fecal calprotectin level for diagnosis of diarrhea likely to have mucosal lesions generated an area under the ROC curve of 0.798 (95% confidence interval [CI]: 0.717-0.879) (Figure 1B). The sensitivity, specificity, PPV, NPV, positive LR, and negative LR of the cutoff values of 50 mg/kg of feces, which was recommended by the American Gastroenterology Association [13], and 708 mg/kg, which was the best cutoff value for this cohort, are shown in Table 3.

At the standard cutoff value of 50 mg/kg of feces, the sensitivity, specificity, and accuracy were 97.8%, 7.8%, and 37.8%, respectively. At this cutoff value, 1 of 45 (2.2%) patients in group A would have been misdiagnosed with diarrhea unlikely to have mucosal lesions, and 83 of 90 (92.2%) patients in group B would have been misdiagnosed with diarrhea likely to have mucosal lesions.

At the cutoff value of 708 mg/kg of feces, the sensitivity, specificity, and accuracy were 71.1%, 78.9%, and 76.3%, respectively; 13 of 45 (28.9%) patients in group A and 19 of 90 (21.1%) patients in group B would have been misdiagnosed (Figure 1).

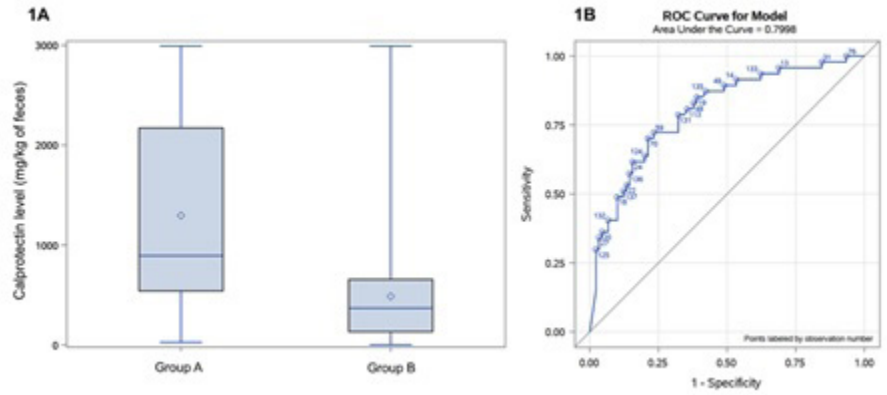


**Figure 1:** The box plot showed fecal calprotectin levels in groups A and B (Figure 1A). The bottom and top of each box represent the 25th and 75th percentiles, giving the interquartile range. The blue line within the box indicates the median, the diamond-shaped figure within the box indicates the mean, and the error bars indicate the 10th and 90th percentiles. Figure 1B shows the receiver operating characteristic (ROC) curve of fecal calprotectin levels for differentiating groups A from B.

**Table 3:** Calprotectin levels in the diagnosis of diarrhea likely to have mucosal lesions

| Cutoff (milligrams per kilograms feces) | Sensitivity | Specificity | PPV | NPV | Positive LR | Negative LR |
|---|---|---|---|---|---|---|
| 50 (standard cutoff value) | 98% | 8% | 35% | 87% | 1.06 | 0.28 |
| 708 (best cutoff value) | 71% | 79% | 63% | 84% | 3.37 | 0.37 |

## 5. Discussion

Fecal calprotectin is a marker used to differentiate inflammatory bowel disease from irritable bowel syndrome in an outpatient setting. However, its benefit in an inpatient setting has not been well studied. This study showed that in this cohort, which comprised mainly the elderly and more than half in an ICU setting, fecal calprotectin was significantly higher in patients with GI infections and ischemic colitis than in patients with diarrhea unlikely to have mucosal lesions; however, the clinical usefulness was limited owing to its poor specificity.

This performance of fecal calprotectin in differentiating nosocomial diarrhea likely and unlikely to have mucosal lesions in this study is consistent with previous studies that compared fecal calprotectin levels between patients with CDI and those with other causes of nosocomial diarrhea.[7-9, 14, 15] The area under the ROC curve was comparable between our study (0.798) and other studies (0.82-0.86) [7, 9, 14], while Barbut et al. reported a lower area under the ROC curve of 0.62 [8]. Interestingly, all studies, including this study, showed considerably overlapping fecal calprotectin levels between the group with and without mucosal lesions, which resulted in only fair test performance, in contrast to its good performance in an outpatient setting. However, the reported fecal calprotectin levels varied in our study and previous studies, particularly those without mucosal inflammation. The median level of fecal calprotectin in our study group with mucosal lesions was 902 mg/kg of feces, whereas the median level ranged from 183-983 mg/kg of feces in patients with CDI in other studies [7-9, 14, 15]. The median level in the group unlikely to have mucosal lesion was 377 mg/kg of feces in our study, while they ranged from <100 to 145 mg/kg of feces in the control groups in other studies [7-9, 14, 15]. This variation may be attributed to differences in patient characteristics between and among cohorts. Our cohort had more than half of the patients in an ICU setting, 75% with tube-feeding nutrition, and almost all patients were receiving antibiotics – all of which could cause mesenteric blood flow disturbance and bacterial dysbiosis, which could result in some degree of microscopic inflammation [16]. Although the fecal calprotectin level differed among studies, many cohorts, including this cohort) reported that the control group's fecal calprotectin level was elevated when using the cutoff used in outpatient settings [8, 14, 15].

Despite the significant difference in fecal calprotectin levels in patients likely and unlikely to have mucosal lesions, this study suggested that fecal calprotectin should not be used in a nosocomial setting. As high as 92% of patients in the group unlikely to have mucosal lesions had the fecal calprotectin level above the standard cutoff value of 50 mg/kg of feces and might have had undergone unnecessary colonoscopy if management decision had been made based on the level of fecal calprotectin. Barnes et al. reported that fecal calprotectin levels rarely changed inpatient management and had no significant difference in the usage of subsequent diagnostic colonoscopy [17].

The strength of this study is that our data were prospectively collected. Moreover, there was no bias in data collection because fecal calprotectin level was not measured until the end of the study after all clinical data had been collected. This study has some limitations. First, the method to diagnose CDI was a PCR-based technique that could detect both colonization and infection [18]. This could explain the low calprotectin levels in some patients with positive C. difficile tests. Second, this study has a relatively small sample size of patients who required a colonoscopy to obtain a definite diagnosis.

In conclusion, fecal calprotectin had suboptimal performance in nosocomial diarrhea compared to the outpatient setting due to significant overlapping levels between the patient likely and unlikely to have mucosal lesions.

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