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ORIGINAL ARTICLE

Stomal calprotectin as a biomarker for assessing Crohn disease activity in patients with stomas

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Key words
inflammatory bowel disease, Crohn disease, calprotectin, ileostomy, biomarker.

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Abstract

Background: Faecal calprotectin is a reliable biomarker for lower gastrointestinal inflammation. However, there are limited data on the utility of calprotectin from stoma effluent.
Aim: The aim of this study was to determine the performance of stomal calprotectin in identifying Crohn disease activity in those with a stoma.
Methods: Patients with Crohn disease and an ileostomy or colostomy were identified from three sites in Australia using a clinical management software. Disease activity was classified based on the presence of inflammation on imaging and/or endoscopy within 3 months of the sample. The primary outcome was the median stomal calprotectin in people with active versus inactive Crohn disease. Other clinical indices, such as C-reactive protein and Harvey Bradshaw Index, were evaluated as a surrogate biomarker for disease activity.
Results: Thirty stomal calprotectin results were identified for 23 patients with paired investigations. Of 30 cases, six had active disease. The median stomal calprotectin in active versus inactive disease were 17 μg/g (interquartile range (IQR) 5–211) and 61 μg/g (IQR 19–105, $P = 0.38$) respectively. Accordingly, stomal calprotectin demonstrated poor sensitivity for active disease (33% at cut-off of 50 μg/g). C-reactive protein was higher for active disease (25, IQR 5–199) compared with inactive disease (5, IQR 2–17, $P = 0.06$), but there was no difference in the Harvey Bradshaw Index (9 (IQR 7–11) vs 5 (3–7), $P = 0.10$).
Conclusion: Stomal calprotectin did not reliably distinguish between active and inactive Crohn disease. C-reactive protein is a more reliable biomarker for disease activity in the setting of ileostomy/colostomy. Further prospective studies are needed to identify more robust biomarkers for detecting inflammation in stoma patients.

Abbreviations: CCCare, Crohn Colitis Care; CD, Crohn disease; CRP, C-reactive protein; CT, computed tomography; GIUS, gastrointestinal ultrasound; HBI, Harvey Bradshaw Index; IBD, inflammatory bowel disease; MRE, magnetic resonance enterography; SC, stomal calprotectin

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Introduction

Advances in the biologic era have improved the management of Crohn disease (CD), yet surgical interventions such as intestinal resection or diversion with stoma formation remain an important option in patients with treatment refractory CD. Approximately 10% of patients with CD require permanent stoma formation, and up to 40% of patients with ileostomies have recurrence of CD by 10 years post total colectomy.[1–3] Furthermore, temporary stomas, such as those used in faecal diversion, play a significant role in managing refractory perianal CD. However, only about 17% of patients undergoing temporary faecal diversion achieve successful restoration of bowel continuity, and of those who undergo stoma reversal, roughly one quarter experience disease relapse requiring re-diversion, further highlighting another subset of patients with CD with prolonged stoma-dependence.[4] Despite this, there are limited data on the accuracy of biomarkers in assessing disease severity in those with CD and a stoma.

Calprotectin is a protein derived predominantly from neutrophils and is a highly sensitive surrogate marker for lower gastrointestinal inflammation when measured in faeces.[5] It is commonly used in clinical inflammatory bowel disease (IBD) practice as a biomarker for disease activity. A recent meta-analysis demonstrated a sensitivity of 80%–92% for faecal calprotectin detecting endoscopically active IBD, depending on the cut-off value.[6] However, these data are from patients without stomas, in whom calprotectin was measured in faeces. Knowledge regarding the performance of stomal calprotectin (SC) is scant.

The aim of this study was to examine the performance of SC in discriminating between active versus inactive CD in stoma effluent.

Methods

This was a retrospective observational multi-centre study involving three large Australian tertiary hospitals with dedicated IBD services: Royal Adelaide Hospital, Liverpool Hospital and St Vincent's Hospital.

Patients with CD and either an ileostomy or colostomy were identified using a prospectively maintained electronic clinical management software called Crohn Colitis Care (CCCare).[7] Only patients with both SC levels and an investigation to identify active CD within 3 months before or after the SC measurement were included. Patients who had CD surgery between the SC and the investigation were excluded. CD activity was classified as active or inactive in accordance with the impression of the reporting radiologist or gastroenterologist using the following investigations: magnetic resonance enterography (MRE), computed tomography (CT), gastrointestinal ultrasound (GIUS) or lower endoscopy via the stoma. Patients could be included multiple times if they had multiple SC samples at different time points.

Demographic, phenotypic and clinical disease parameters were collected, including Montreal phenotype, Harvey–Bradshaw Index (HBI) and C-reactive protein (CRP). Any missing data on CCCare were searched for within hospital-owned electronic medical record systems used at individual sites.

The primary outcome was the median SC in active versus inactive disease. Secondary (exploratory) outcomes included the sensitivity, specificity, positive predictive value and negative predictive value of SC at cut-offs of 50, 100 and 150 μg/g; the above measurements for the individual cohorts of patients with ileostomy or colostomy; and the correlation between SC and other clinical indices (CRP, HBI).

The median SC values for active and inactive disease were compared using Mann–Whitney tests. Fisher's exact test was used to compare proportions and determine sensitivity and specificity. Correlations were derived using Pearson r for normally distributed data and Spearman r for non-normally distributed data. Statistical analysis was performed using GraphPad Prism (version 9, San Diego, CA, USA). The study was approved by the human research and ethics committees at each institution.

Results

Out of 113 patients identified with CD and a stoma, 30 SC results from 23 patients met the inclusion criteria of having a paired objective investigation within 3 months of the sample (Fig. 1, Table 1). Of the 30 SC results, 23 samples (from 17 patients) were from ileostomies, and seven samples (from six patients) were from colostomies. The median time between SC samples of patients who had more than one sample was 386 days (interquartile range (IQR) 285–585). The median time between SC and the objective investigation was 18 days (IQR 8–41). Six of the 30 measurement episodes (20%) were deemed to be during active disease (according to paired objective data).

The median SCs for active and inactive disease were 17 μg/g (IQR 5–211) and 61 μg/g (IQR 19–105, $P = 0.38$) respectively (Fig. 2). Sub-analysis of SCs from ileostomies only ($n = 23$), SCs in which non-CT objective testing was available ($n = 22$), and SCs with objective testing within 6 weeks ($n = 22$) yielded similar results (Table S1, Fig. S1). The sensitivity of SC for detecting active disease at cut-off <50 μg/g was 33%, <100 μg/g was 17% and <150 μg/g was 17% (Table 2).

CRP and HBI were available for 27 and 14 patients respectively. The median CRP for active disease was

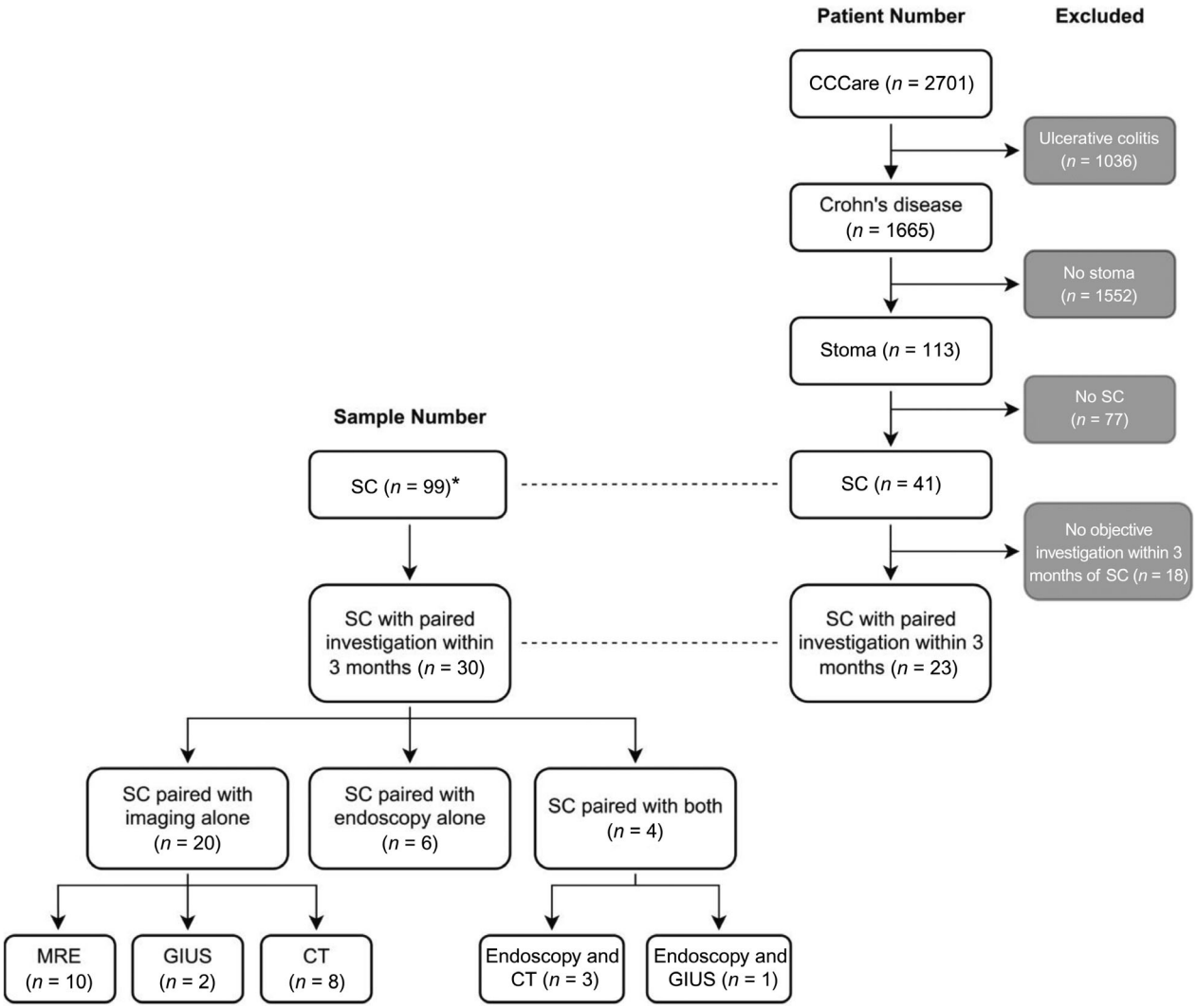

Figure 1 Consort diagram. From a total of 2701 patients on inflammatory bowel disease management software, Crohn Colitis Care (CCCare), only 23 patients were eligible for the study correlating to a final stomal calprotectin sample size of 30 samples. Reasons for exclusion from study are shown. CT, computed tomography; GIUS, gastrointestinal ultrasound; MRE, magnetic resonance enterography; SC, stomal calprotectin. *Ninety-nine SC samples represent 41 individual patients (i.e. some patients have multiple stomal calprotectin samples).

25 (5–199) versus 5 (2–17, $P = 0.06$) for inactive disease. The median HBI was 9 (7–11) versus 5 (3–7, $P = 0.10$) respectively. There was no correlation between SC and CRP (Spearman $r = -0.03$, $P = 0.89$) or with HBI (Pearson $r = 0.04$, $P = 0.88$) (Fig. S2,S3). The sensitivity of CRP at cut-off <3 mg/L was 100%, <5 mg/L was 83% and <8 mg/L was 67% (Table S2). The sensitivity of HBI at cut-off <5 was 100% (Table S3).

Discussion

In this multicentre Australian cohort of CD patients with stomas, there was no difference in median SC in patients with active disease compared with those with inactive disease. Numerically, the median SC was paradoxically lower in those with active inflammation compared to patients with inactive disease, although this difference was not statistically significant. Despite the modest sample size, this project provides additional insights into the limited literature on this novel biomarker.

We included patients with both ileostomies and colostomies in this study, given it is not clear whether resection of part of the colon (in the setting of a colostomy) may influence calprotectin performance. However, since these may represent two different environments for calprotectin release, we analysed the results for SC performance in ileostomy patients only, and again found no difference in performance between

Table 1 Patient demographics ($n = 23$ patients)

Sex, *n* (%)	
Male	11 (48%)
Female	12 (52%)
Age at time of SC sample, median (IQR)	40 (32–55)
Montreal classification of CD, *n* (%)	
Age at diagnosis	
A1 (<16 years)	3 (14%)
A2 (17–40 years)	11 (52%)
A3 (>40 years)	7 (33%)
CD location	
L1 (Ileal)	3 (14%)
L2 (colonic)	4 (19%)
L3 (ileocolonic)	14 (67%)
CD behaviour†	
B1 (non-stricturing, non-penetrating)	5 (24%)
B2 (stricturing)	4 (33%)
B3 (penetrating)	9 (57%)
B2 + B3 (stricturing, penetrating)	3 (14%)
P1 (peri-anal disease)	10 (48%)
Type of stoma, *n* (%)	
Ileostomy	17 (74%)
Colostomy	6 (26%)
Crohn disease activity, *n* (%)‡	
Active disease	6 (26%)
Inactive disease	17 (74%)
C-reactive protein (mg/L), median (IQR)§	6 (3–30)
Harvey Bradshaw Index, median (IQR)¶	6 (4–7)

†Percentages for Crohn disease behaviour are accumulatively >100% as patients may have more than one behaviour phenotype.
‡For patients who were represented more than once, only the first classification of Crohn disease activity was included.
§For patients who were represented more than once, only the first C-reactive protein sample was included.
¶For patients who were represented more than once, only the first Harvey Bradshaw Index data were included.
CD, Crohn disease; IQR, interquartile range; SC, stomal calprotectin.

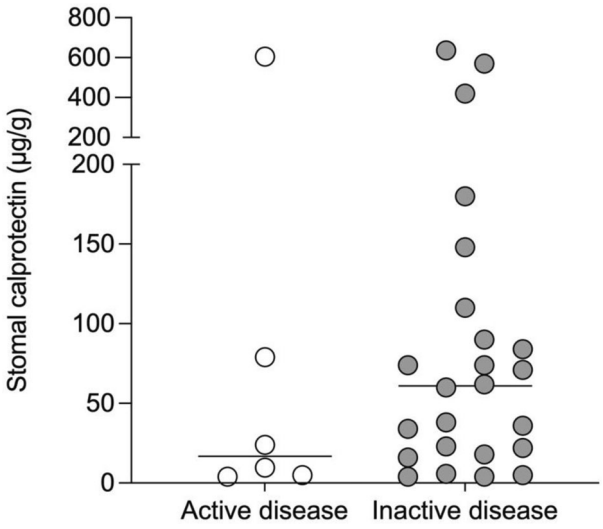

Figure 2 Median stomal calprotectin for active disease versus inactive disease ($n = 30$). Inactive disease paradoxically had a higher median stomal calprotectin than active disease numerically, but not to statistical significance. Bars represent median value. Mann–Whitney test, $P = 0.38$.

Table 2 Performance of differing stomal calprotectin cut-offs for detecting active disease versus inactive disease

SC	Sensitivity	Specificity	PPV	NPV
<50 µg/g	33%	46%	13%	73%
<100 µg/g	17%	75%	14%	78%
<150 µg/g	17%	83%	20%	80%

NPV, negative predictive value; PPV, positive predictive value; SC, stomal calprotectin.

active and inactive disease. We did not have information regarding stoma health. Unhealthy or inflamed stomas, along with trauma to the stoma, may contribute to falsely elevated SC levels in patients with inactive disease.

Daoud *et al.* demonstrated a strong correlation between SC and ileoscopy or imaging (CT and MRE).[8] This study, in comparison to ours, had more samples from ileostomies only (51 vs 23) and, at similar SC cut-offs, demonstrated higher sensitivity (88% for SC >60 µg/g vs 33% for SC >50 µg/g) and specificity (91% for SC >60 µg/g vs 26% for SC >50 µg/g), despite having a similar demographic of Montreal classification and proportion with active disease (31% vs 26% respectively). This may be due to the high proportion of objective testing by CT alone in this study (53%) in comparison to ours (27%). Although more convenient, CT alone may be inadequate in assessing for inflammation and can overcall inflammation when it is not actually present.

There have been two similar studies published in abstract form only at the current time of writing. In an abstract of 29 patients, Bouri *et al.* demonstrated sensitivity and specificity for SC >50 µg/g of 80% and 47% respectively.[9] However, the majority of these patients had intestinal failure (as the institution was a high-level quaternary hospital), which is a rare entity in CD and is not directly applicable to the broad CD demographic.

Meanwhile, a Korean abstract evaluated the performance of calprotectin from 166 ileostomy samples as compared with contemporaneous imaging/endoscopy.[10] A large proportion of these cases had active inflammation (112, 67%), and the median calprotectin was higher in those with inflammation compared with those without (196 vs 29.9 µg/g, $P < 0.001$), but without any difference in CRP. They reported a cut-off of 59 µg/g as a strong predictor for the presence or absence of small bowel inflammation. However, the abstract did not detail

Internal Medicine Journal **55** (2025) 461–466

the specific methods used to determine inflammation (e.g. imaging, endoscopy), nor did it specify the type of imaging (e.g. MRE, CT). Therefore, the data should be interpreted with caution; however, we eagerly await the full peer-reviewed publication.

Nevertheless, our study is at odds with the three studies mentioned above, where the researchers found a difference in SC values in those with inflammation versus those with inactive disease, whereas we did not. This may represent the lower number of cases in our study where active inflammation was present ($n = 6$). This likely reflects the true nature of patients with CD and stomas (an ileostomy can be a 'cure' for many) but also limits the power of the study to detect meaningful results. Alternatively, it is possible inflammation may have been overcalled depending on the method used to determine this. For example, in the Korean abstract,[10] bowel wall thickening on imaging could be used as a determinant of active inflammation; however, particularly in the absence of contrast enhancement, this can represent past (but inactive) inflammation. In our study, we used stringent methods to determine active inflammation, where MRE, GIUS and endoscopy are reasonably robust investigations, and only eight (27%) were evaluated using CT alone (Fig. 1). Finally, it is also possible that, as suggested in our paper, calprotectin might not consistently serve as a reliable marker of inflammation in the setting of a stoma.

We also analysed the performance of CRP and HBI as markers for active disease. While the difference between median CRP in active versus inactive CD was not statistically significant, this may have been a type 2 error with small sample size. Indeed, at their respective cut-offs, CRP exhibited higher sensitivity but lower specificity in comparison to SC at detecting active disease, indicating that CRP may be a more effective screening tool for CD activity. However, since SC is typically tested only in the presence of symptoms, evaluating its performance as a routine screening tool is challenging.

HBI demonstrated high sensitivity (100%) but low specificity (38%) for active disease, highlighting the frequently observed discrepancy between symptoms and disease activity. HBI includes variables that are difficult to quantify in the setting of a stoma, such as number of soft/liquid stools per day. Developing a tailored clinical index for assessing disease activity in patients with stomas would more accurately evaluate CD severity in these cohorts.

Limitations of this study include the small sample size, despite their derivation from three large tertiary IBD centres, and the retrospective nature of the analysis. Conversely, clinical data such as clinical indices (HBI, stoma surgery, disease phenotype) and investigations were collected prospectively through a uniform system which is a strength of this study. Disease activity was not evaluated using a consistent measure, and using a single-objective measure would likely improve accuracy. Most cases of CD recurrence in patients with an ileostomy occur distally and within the range of ileoscopy, so future prospective studies should primarily incorporate ileoscopy. Additionally, standardised reporting methods would enhance the ability to assess disease severity. The small number of cases with active inflammation among the group likely reflects the true nature of CD patients with stomas (an ileostomy can often be a 'cure' for many), but this also limits the study's ability to detect meaningful results.

Conclusion

In conclusion, our study did not support the use of SC as a biomarker for disease activity in patients with CD and a stoma. This may be attributed to limitations such as the small sample size and the use of varying comparative objective measures with limited ileoscopy. Nevertheless, the study provides additional insights into the relationship between SC and CD activity, or possibly the lack thereof, and underscores the need for a standardised approach to evaluating this biomarker in future research. Furthermore, current clinical indices, such as HBI (and Crohn Disease Activity Index), are suboptimal for patients with a stoma, highlighting the need for a specific clinical index for this population.

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Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web-site:

Table S1. Comparative table of median SC for active disease and inactive disease using various sub-analysis
Table S2. Performance of differing C-reactive protein cut-offs for detecting active disease versus inactive disease
Table S3. Performance of Harvey–Bradshaw Index at cut-off <5 for detecting active disease versus inactive disease
Figure S1. Median stomal calprotectin among patients with ileostomy
Figure S2. Correlation between stomal calprotectin and C-reactive protein
Figure S3. Correlation between stomal calprotectin and Harvey–Bradshaw Index