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► **To cite this version:**

Abderrahim Oussalah, Valérie M. Laurent, Olivier Bruot, Jean-Louis Gueant, Denis Régent, et al..
Additional benefit of procalcitonin to C-reactive protein for assessing disease activity and severity in
Crohn's disease. *Alimentary Pharmacology and Therapeutics*, 2010, 32 (9), pp.1135. 10.1111/j.1365-
2036.2010.04459.x . hal-00577004

HAL Id: hal-00577004

<https://hal.science/hal-00577004v1>

Submitted on 16 Mar 2011

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**Additional benefit of procalcitonin to C-reactive protein for
assessing disease activity and severity in Crohn's disease**

Journal:	<i>Alimentary Pharmacology & Therapeutics</i>
Manuscript ID:	APT-0611-2010.R1
Wiley - Manuscript type:	Original Scientific Paper
Date Submitted by the Author:	26-Aug-2010
Complete List of Authors:	Oussalah, Abderrahim; University Hospital of Nancy, Inserm, U954 and Department of Hepato-Gastroenterology LAURENT, Valérie; University Hospital of Nancy, Departement of Radiology BRUOT, Olivier; University Hospital of Nancy, Departement of Radiology GUEANT, Jean-Louis; INSERM U954 Régent, Denis; University Hospital of Nancy, Departement of Radiology BIGARD, Marc-André; UNIVERSITY HOSPITAL BRABOIS, Gastroenterology Peyrin-Biroulet, Laurent; University Hospital of Nancy, Hepato-gastroenterology
Keywords:	Crohn's disease < Disease-based, Inflammatory bowel disease < Disease-based, Ulcerative colitis < Disease-based, Inflammation < Topics

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Additional benefit of procalcitonin to C-reactive protein for assessing disease activity and severity in Crohn's disease

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Running title: Procalcitonin in inflammatory bowel diseases

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Keywords: serum procalcitonin level; Crohn's disease; ulcerative colitis; inflammatory
bowel diseases.

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ABSTRACT

Background:

Serum procalcitonin level (SPL) may reflect non-infectious inflammation.

Aim:

To assess the correlation of SPL with clinical, biological, endoscopic and radiological markers of disease activity in inflammatory bowel diseases (IBD) and to evaluate the additional diagnostic benefit of measuring SPL to that of C-reactive protein (CRP) for disease activity appraisal.

Methods:

We performed a prospective observational study. Spearman's rank correlation and receiver operating characteristic analysis were used to evaluate correlation and diagnostic accuracy, respectively.

Results:

In Crohn's disease (CD) (n=30), SPL was strongly correlated with clinical, biological, endoscopic and radiological disease activity markers. In CD, a SPL >0.14 µg/L demonstrated a high accuracy for detecting severe disease (Sensitivity=100%; Specificity=96%; AUROC=0.963; P=0.0001). The diagnostic accuracy of the 'SPL-CRP strategy' (CRP >5 mg/L and SPL >0.05 µg/L) was significantly superior to that of CRP alone for diagnosing severe CD (AUROC=0.783 versus 0.674; P=0.01). In ulcerative colitis (UC) (n=27), SPL was correlated with CRP and with endoscopic and radiological disease activity markers.

Conclusions:

In CD, the SPL was correlated with all disease activity markers and a cut-off of 0.14 µg/L could distinguish severe forms of the disease. The 'SPL-CRP strategy' was superior to CRP alone for diagnosing active or severe CD.

INTRODUCTION

Procalcitonin, a prohormone of 116 amino acids is the precursor for the calcium homeostasis hormone, calcitonin, which is found in the thyroid C cells and the pulmonary endocrine cells.¹

It has been found to circulate at very low concentrations in normal serum and is presumably produced by the neuroendocrine cells in the thyroid gland and in the lungs.¹ Procalcitonin plays a major role in systemic inflammation and induces a dose-dependent increase in TNF α secretion.² In a study on blood of normal human volunteers, recombinant human procalcitonin had an inhibitory effect on leukocyte migration with marked malfunction of neutrophils that is known to occur during sepsis.² Data from experimental models demonstrated that human recombinant procalcitonin induced a dose-dependent increase in leukocyte-derived tumour necrosis factor alpha (TNF α) secretion from isolated lymphocytes.² Current evidences indicate that mediators such as TNF α , as well as interleukin (IL)-1b and IL-6, comprise the specific proximate stimuli to hyperprocalcitonaemia.^{3, 4} TNF α is a potent stimulant of procalcitonin production and may further reinforce the procalcitonin levels in a self-perpetuating cascade fashion.^{3,4}

Multiple studies have demonstrated that serum levels of procalcitonin are markedly increased in humans with severe infection.⁵ Procalcitonin has also evaluated in chronic inflammatory and autoimmune conditions as a marker of disease activity.⁶⁻⁸ Interestingly, in patients with Wegener's granulomatosis serum procalcitonin level (SPL) was markedly elevated in patients with highly active disease in comparison with those with inactive disease.⁶ In children with active autoimmune processes, slight elevation of procalcitonin concentration was observed without any evidence of bacterial infection.⁷

In patients with inflammatory bowel diseases (IBD), the association of procalcitonin with disease activity remains poorly investigated. Two studies in IBD patients demonstrated that procalcitonin had good diagnostic value for differentiating flares of IBD from self-limited

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3 colitis, but found conflicting results when evaluating procalcitonin as a biological marker of
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5 disease activity.^{9, 10} Only one study evaluated the diagnostic value of SPL in determining
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7 disease activity in IBD, but included a relative small number of patients with Crohn's disease
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9 (CD), which prevents to draw conclusions.¹¹ Furthermore, none of the aforementioned studies
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11 evaluated the correlation of procalcitonin with endoscopic and radiological markers of IBD
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13 activity.⁹⁻¹¹ Finally, the additional diagnostic benefit of SPL evaluation to that of C-reactive
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15 protein (CRP) has never been evaluated in IBD.
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20 The aims of this study was therefore to assess for the first time the correlation of SPL with
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22 clinical, biological, endoscopic and radiological markers of disease activity in patients with
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24 IBD and to evaluate the additional diagnostic benefit of measuring SPL to that of CRP in the
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26 assessment of disease activity in IBD.
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30 31 32 **MATERIALS AND METHODS**

33 34 **Study design**

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36 We performed an observational study of a single-centre cohort. Data were retrieved from a
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38 prospectively maintained database.
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41 42 43 **Population studied**

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45 All consecutive patients seen between January 15, 2008 and June 1, 2010 who had
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47 concomitant clinical, biological, and radiological evaluation with or without concomitant
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49 colonoscopy during an IBD flare or to rule out active disease were included in the study. All
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51 investigations were prescribed at the discretion of the physician. Patients were included in the
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53 analysis if an intercurrent infection was ruled out by stool analysis for enteric pathogens and
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55 *Clostridium difficile* toxin, and quantitative real-time polymerase chain reaction in colonic
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57 biopsies for the detection of active cytomegalovirus infection in patients with severe or
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steroid-refractory colitis. Our cohort of IBD patients is reported to *The Commission Nationale de l'Informatique et des Libertés* (N°1404720) which supervises the implementation of the January 6, 1978 Act on data processing, data files, and individual liberties as amended by the August 6, 2004 Act relating to protection of individuals with regard to the processing of personal data.

Clinical and biological markers of disease activity

Clinical disease activity scores were calculated using data collected on the day of patient's morphological evaluation: the simple clinical colitis activity index (SCCAI)¹² and Truelove and Witts severity index¹³ in ulcerative colitis (UC) patients, and the Crohn's Disease Activity Index (CDAI)¹⁴ in CD patients. The following biological parameters were collected from electronic patients' records: serum procalcitonin, CRP, haemoglobin, hematocrit, leukocytes, platelets, albumin, and serum iron. Of note, procalcitonin is routinely used in our department to rule out superimposed infection in all hospitalized patients with IBD. SPL are measured using automated immunofluorescent assays of procalcitonin in human serum or plasma (EDTA, heparin) samples (Brahms PCT sensitive KRYPTOR kit for Brahms KRYPTOR, Hennigsdorf, Germany) according to the supplier's protocol. **Normal SPL was defined as <0.05 µg/L according to supplier's reference values and normal CRP level was defined as <5 mg/L.**

Endoscopy

All colonic lesions were rated according to standardized scoring systems for UC and CD as routinely used in the department. In patients with UC, the severity and extent of endoscopic lesions were assessed by the Modified Baron score.¹⁵ Five endoscopic segments were defined: rectum, sigmoid, left colon, transverse colon, and right colon. The Modified Baron score was

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3 applied to each segment to obtain a segmental Modified Baron score. A total score was
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5 calculated from the sum of the segmental scores to obtain the total Modified Baron score. In
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7 patients with CD, the severity of endoscopic lesions was assessed by the Simplified
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9 Endoscopic Activity Score for Crohn's Disease (SES-CD).¹⁶ Colonoscopy was considered
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11 concomitant to MR-DWI-colonography if it was performed within 48 hours after the
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13 radiological examination, without any therapeutic intervention during this interval.
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18 19 20 **Magnetic resonance colonography**

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22 The morphological evaluation of IBD patients consisted of a magnetic resonance diffusion-
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24 weighted imaging colonography (MR-DWI-colonography) without oral or rectal preparation
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26 and with or without concomitant colonoscopy as described previously.¹⁷ Radiological
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28 evaluation of disease activity was evaluated by the 6-items Magnetic resonance score (MR-
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30 score).¹⁷ The MR-score includes six radiological signs: 1) DWI hyperintensity, 2) rapid
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32 gadolinium enhancement after intravenous contrast medium administration, 3) differentiation
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34 between the mucosa-submucosa complex and the muscularis propria, 4) bowel wall
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36 thickening, 5) parietal oedema, and 6) the presence of ulceration(s). The definition of each
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38 radiological sign of the MR-score is provided as supplementary material (**Supplemental** Table
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40 **1 online**). The presence and absence of a radiological sign in a given segment were rated '1'
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42 and '0', respectively. The segmental MR-score (MR-score-S) was calculated as the sum of the
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44 numerical values obtained for the six radiological signs for a given segment. The total MR-
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46 score (MR-score-T) was calculated as the sum of the MR-score-S in a patient, with values
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48 ranging from 0 to 30 in the case of UC and from 0 to 36 in the case of CD.
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Definition of active and severe disease

In order to achieve a pooled analysis, IBD patients were considered to have an active disease if they had a CDAI ≥ 150 in case of CD and in case of UC if they had 'mild', 'moderate' or 'severe' UC according to Truelove and Witts severity index¹³, and a SCCAI >5 .¹⁸ Patients were considered to have severe disease if they have a CDAI ≥ 300 or a 'severe' UC according to Truelove and Witts severity index.¹³

Statistical analyses

Quantitative variables are described as means and standard deviation (S.D.) or as medians and percentiles (I.Q.R. for Inter Quartile Range: 25-75th) in the case of an abnormal distribution. Proportions are expressed as percentages and 95% confidence intervals. All correlations were studied using Spearman's nonparametric correlation coefficients. The diagnostic accuracy of serum procalcitonin ($\mu\text{g/L}$) for detecting severe forms of IBD was evaluated using receiver operating characteristic (ROC) analysis according to DeLong et al¹⁹ to calculate the sensitivity, specificity, positive, and negative predictive values, and area under the receiver operating characteristic curve (AUROC) with the associated *P*-value. The comparison of AUROCs was carried out using the procedure proposed by DeLong et al.¹⁹ The comparison of serum procalcitonin values between different groups of disease activity was performed using the Kruskal-Wallis test. All the reported *P*-values were two-sided, and *P*-values of <0.05 were considered statistically significant. Statistical analyses were performed using MedCalc software, version 11.3.3.0 (MedCalc Software, Mariakerke, Belgium).

RESULTS

Between January 15, 2008 and June 1, 2010, 57 patients with a diagnosis of IBD underwent clinical, biological, endoscopic, histological and/or radiologic evaluation and could be included in the analysis. The baseline characteristics of included patients with CD (n=30) or UC (n=27) are shown in Tables 1 and 2, respectively.

Whole IBD cohort (n=57)

Comparison of serum procalcitonin levels between active and inactive inflammatory bowel diseases

The median value of SPL was significantly higher in patients with active IBD (0.10 µg/L; IQR 25-75th, 0.07 to 0.21) in comparison to those with inactive disease (0.07 µg/L; IQR 25-75th, 0.06 to 0.08) ($P = 0.02$) (Figure 1A). Consistently, patients with CRP level >5 mg/L exhibited significantly higher SPL (0.11 µg/L; IQR 25-75th, 0.07 to 0.21) when compared with patients with a CRP level ≤5 mg/L (0.06 µg/L; IQR 25-75th, 0.06 to 0.07) ($P = 0.002$) (Figure 1B).

Correlation of serum procalcitonin level with biological and radiological markers of disease activity

SPL was strongly correlated with CRP ($r=0.592$, $P < 0.001$) (Figure 2), albumin ($r=-0.609$, $P < 0.001$), haemoglobin ($r=-0.500$, $P < 0.001$), and MR-score ($r=0.552$, $P < 0.001$) and was significantly correlated with serum iron ($r=-0.283$; $P = 0.03$) and platelets ($r=0.393$, $P = 0.003$). SPL was not correlated with leukocytes ($r=0.1$, $P = 0.5$).

In the whole group of IBD patients, SPL was significantly correlated with CRP in patients with active disease (Supplemental Table 2 online). In patients with inactive IBD, SPL and

CRP were not significantly correlated; however, this result is not reliable due to the risk of type II error related to the small sample size (n=13).

Crohn's disease

Correlation of serum procalcitonin level with clinical, biological, endoscopic and radiological markers of activity

In patients with CD (n=30), SPL was strongly correlated with all disease activity markers namely, CDAI (r=0.545, $P = 0.002$), CRP (r=0.626, $P = 0.0002$) (Figure 2), albumin (r=0.813, $P < 0.0001$), haemoglobin (r=-0.709, $P < 0.0001$), SES-CD (r=0.797, $P = 0.0006$), and MR-score (r=0.599, $P = 0.0005$) (Table 3). SPL was significantly correlated with CRP in patients with active CD as opposed to patients in remission (Supplemental Table 2 online).

Diagnostic accuracy of serum procalcitonin for detecting disease activity

In patients with CD, using ROC analysis, a SPL >0.14 $\mu\text{g/L}$ demonstrated a high accuracy for detecting severe disease as defined by a CDAI ≥ 300 with a sensitivity of 100%, a specificity of 96%, positive and negative predictive values of 88% and 100%, respectively, and an AUROC of 0.963 (95% Confidence Interval (CI), 0.822 to 0.999; $P = 0.0001$) (Table 4 and Figure 3). In CD patients, SPL >0.14 $\mu\text{g/L}$ had a sensitivity of 67%, a specificity of 100%, and an AUROC of 0.815 (95% CI, 0.631 to 0.932; $P = 0.0005$) for detecting patients with a CRP >30mg/L (Table 4). Consistently, the median SPL was significantly higher in patients with a CDAI ≥ 300 (0.21 $\mu\text{g/L}$; IQR 25-75th, 0.19 to 0.30) compared with those with a CDAI <300 (0.07 $\mu\text{g/L}$; IQR 25-75th, 0.05 to 0.07) ($P = 0.0002$).

In comparison with a CRP cut-off of 5 mg/L, a SPL cut-off of 0.05 $\mu\text{g/L}$ had the same diagnostic accuracy (AUROC) for detecting active or severe CD ($P = 0.90$ and $P = 0.77$, respectively). However, the combination of CRP cut-off of 5 mg/L with a SPL cut-off of 0.05

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3 $\mu\text{g/L}$, called the 'SPL-CRP strategy', yielded a better specificity for diagnosing active or
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5 severe CD (Table 5). Moreover, the diagnostic accuracy of the SPL-CRP strategy was
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7 significantly superior to that of CRP alone for diagnosing severe CD with an AUROC of
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9 0.783 versus 0.674 ($P = 0.01$) (Table 5 and Figure 4).
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12 13 14 15 **Ulcerative colitis**

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17 *Correlation of serum procalcitonin level with clinical, biological, endoscopic and*
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19 *radiological markers of activity*

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21 In patients with UC ($n=27$), SPL was correlated with the SCCAI ($r=0.423$, $P = 0.03$), CRP
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23 level ($r=0.548$, $P = 0.003$) and MR-score ($r=0.536$, $P = 0.004$). By contrast, SPL were not
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25 correlated with albumin, haemoglobin, and the total modified Baron score (Table 3). SPL was
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27 significantly correlated with CRP in patients with active UC as opposed to patients with
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29 inactive UC (Supplemental Table 2 online).
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36 *Diagnostic accuracy of serum procalcitonin for detecting disease activity*

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38 In patients with UC, ROC analysis did not reveal any significant threshold of SPL for the
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40 detection of active or severe disease ($P = 0.08$ and $P = 0.2$, respectively) (Table 6). The SPL-
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42 CRP strategy did not yield a better accuracy for diagnosing active or severe UC in
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44 comparison with CRP alone (Table 5).
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50 51 **DISCUSSION**

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53 This is the first study showing that SPL is correlated with clinical, biological, endoscopic
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55 and/or radiological disease activity in patients with IBD. To date three studies have evaluated
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57 procalcitonin in IBD.⁹⁻¹¹ By pooling UC and CD patients, we found that SPL was
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59 significantly higher in patients with active IBD. These results are in line with those of a
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3 previously reported study.⁹ Consistently, by pooling UC and CD patients, SPL was
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5 significantly higher in patients with a CRP >5 mg/L and was correlated with CRP levels. This
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7 finding is also in line with the study by Oruc et al. that demonstrated a significant correlation
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9 between SPL and CRP in patients with IBD.¹¹
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12 When considering only patients with CD, Herrlinger et al. demonstrated that SPL were
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14 significantly correlated with the CDAI, while no correlation was found with CRP level.⁹ By
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16 contrast, in the study by Thia et al., SPL showed no correlation with CD activity using the
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18 Harvey-Bradshaw index (HBI).¹⁰ This discrepancy may be partly explained by the fact that
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20 CD activity has been scored with the HBI in the study by Thia et al.,¹⁰ conversely to our study
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22 and that of Herrlinger et al.⁹ that used the CDAI as CD activity score. In the study by Oruc et
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24 al., SPL was not correlated with CDAI.¹¹ However, this study included only nine CD
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26 patients, which prevents any conclusion. It is noteworthy that none of the three studies⁹⁻¹¹ had
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28 evaluated endoscopic or radiological markers of disease activity.
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33 Our study showed that in patients with UC, SPL was correlated with the SCCAI, CRP, and
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35 the MR-score score, whereas no correlation was found with endoscopic disease activity
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37 scores. Among the three studies that evaluated SPL in IBD patients,⁹⁻¹¹ only one has
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39 specifically evaluated the SPL in the subgroup of patients with UC, and did not show any
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41 correlation between SPL and clinical disease activity.¹⁰ This difference may be partly
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43 explained by the fact that UC activity has been scored with the Physician Global
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45 Assessment²⁰ in the study by Thia et al.,¹⁰ conversely to our study that used the SCCAI which
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47 is a well validated disease activity index for UC.^{21, 22}
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53 In the study by Oruc et al. a procalcitonin cut-off value of 0.05 µg/L, found in ROC analysis,
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55 had a poor accuracy (sensitivity, 67%; specificity 42%) for detecting active IBD as defined by
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57 a CDAI >150 or a 'moderate' or 'severe' UC according to Truelove and Witts severity
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59 index.¹³ Importantly, by using ROC analysis, we were able to identify a SPL cut-off of 0.14
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3 $\mu\text{g/L}$ as having a high accuracy (sensitivity, 100%; specificity, 95%) for detecting severe
4 forms of CD as defined by a CDAI ≥ 300 . Interestingly, by adding SPL measurement to
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6 routine CRP evaluation (The SPL-CRP strategy), we were able to double the specificity of the
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8 SPL-CRP strategy for diagnosing active or severe forms of CD when compared to a 'CRP
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10 alone'-based strategy.
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15 Overall, we found that the performance of procalcitonin for evaluating disease activity was
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17 weaker in UC compared with CD. Consistently, there was no cut-off value for SPL capable of
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19 detecting severe forms of UC in our study. This is in line with previous reports.^{9, 10}
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22 From a mechanistic point of view one can speculate that the best correlation of procalcitonin
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24 with the degree of activity of CD is linked to the fact that $\text{TNF}\alpha$ plays a central role in the
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26 pathogenesis of this disease.
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29 In conclusion, our results indicate that procalcitonin might be useful in clinical practice to
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31 assess disease activity in patients with CD. Notably, we demonstrated for the first time that
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33 SPL was correlated with endoscopic and radiological markers of activity in CD, and with
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35 radiological activity in UC. In patients with CD, a threshold of 0.14 $\mu\text{g/L}$ for procalcitonin
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37 may detect the most severe forms of the disease. The combination of procalcitonin with CRP
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39 would be more efficient than CRP alone for the diagnosis of active or severe CD. Our results
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60 need to be confirmed in independent studies.

ACKNOWLEDGEMENTS

1. Authors' declaration of personal interests: AO, VL, OB, JLG, DR, MAB, and LPB declare no conflict of interest.
2. Declaration of funding interests: This work did not receive any financial support.

For Peer Review

Table 1. Baseline characteristics of patients in the Crohn's disease group (n=30)

Crohn's disease (n=30)	n	%
Montreal classification		
A1 (below 16 years)	3	10
A2 (between 17 and 40 years)	20	67
A3 (above 40 years)	7	23
B1 (non-stricturing, non penetrating)	18	60
B2 (stricturing)	7	23
B3 (penetrating)	5	17
L1 (isolated ileal disease)	8	27
L2 (isolated colonic disease)	14	47
L3 (ileocolonic disease)	8	27
L4 (concomitant upper gastrointestinal disease)	2	7
P (concomitant perianal disease)	12	40
Concomitant medication(s)^a		
Mesalamine	8	27
Oral or intravenous corticosteroids	11	37
Azathioprine	10	33
Methotrexate	1	3
Tumour Necrosis Factor antagonists	5	17
Male gender	11	37
Tobacco use	9	30
Previous abdominal IBD-related surgery	10	33
	Mean	Standard deviation
Patient age at IBD diagnosis (years)	32	15
Patient age at inclusion (years)	38	16
Haemoglobin (g/dL)	12.0	2.0
Hematocrit (g/dL)	35.8	5.5
Platelets (x 10 ⁹ /L)	402	129
Albumin (g/L) (n=18)	34.8	8.9
Serum iron (mg/L)	0.54	0.39
Crohn's disease activity index ^b	213	138
SES-CD ^c (n=14)	12	11
	Median	IQR 25-75th
Disease duration at inclusion (months)	40	19 to 109
C-reactive protein (mg/L)	15.9	4.3 to 64.4
Leukocytes (x 10 ⁹ /L)	9.510	7.720 to 12.030
Magnetic-Resonance score (0-36) ^d	10	6 to 15

NOTE. IBD: Inflammatory bowel diseases; SES-CD: Simplified Endoscopic Activity Score for Crohn's Disease; IQR: Interquartile range 25-75th percentile.

^aA patient may receive more than one concomitant medication

^bClinical evaluation of disease activity

^cEndoscopic evaluation of disease activity

^dRadiological evaluation of disease activity

Table 2. Baseline characteristics of patients in the ulcerative colitis group (n=27)

Ulcerative colitis (n=27)	n	%
Ulcerative colitis topography according to Montreal classification		
E1 (Ulcerative proctitis)	1	4
E2 (Left sided ulcerative colitis)	7	26
E3 (Extensive ulcerative colitis)	19	70
Concomitant medication(s)^a		
Mesalamine	10	37
Oral or intravenous corticosteroids	10	37
Azathioprine	7	26
Methotrexate	0	–
Cyclosporine	4	15
Tumour Necrosis Factor antagonists	6	22
Male gender	14	52
Tobacco use	2	7
Previous abdominal IBD-related surgery	0	–
	Mean	Standard deviation
Patient age at inclusion (years)	37	14
Haemoglobin (g/dL)	11.3	2.1
Hematocrit (g/dL)	34.0	5.9
Leukocytes (x 10 ⁹ /L)	9.200	3.708
Platelets (x 10 ⁹ /L)	430	151
Albumin (g/L) (n=24)	32.3	8.0
Simple clinical colitis activity index ^b	7	4
Total modified Baron score ^c (n=15)	8	5
Magnetic-Resonance score (0-30) ^d	18	8
	Median	IQR 25-75th
Patient age at IBD diagnosis (years)	28	23 to 36
Disease duration at inclusion (months)	58	19 to 127
C-reactive protein (mg/L)	14.2	6.0 to 38.0
Serum iron (mg/L)	0.33	0.21 to 0.64

NOTE. IBD: Inflammatory bowel diseases; IQR: Interquartile range 25-75th percentile.

^aA patient may receive more than one concomitant medication

^bClinical evaluation of disease activity

^cEndoscopic evaluation of disease activity

^dRadiological evaluation of disease activity

Table 3. Correlation of serum procalcitonin concentration ($\mu\text{g/L}$) with clinical, biological, endoscopic and radiological markers of disease activity in patients with inflammatory bowel disease

	CD group (n=30)			UC group (n=27)		
	ρ^a	95% CI	<i>P</i> -value ^a	ρ^a	95% CI	<i>P</i> -value ^a
Clinical marker of disease activity						
Crohn's disease activity index	0.545	0.230 to 0.757	0.002	–	–	–
Simple clinical colitis activity index	–	–	–	0.423	0.051 to 0.692	0.03
Biological markers of disease activity						
C-reactive protein (mg/L)	0.626	0.343 to 0.805	0.0002	0.548	0.212 to 0.768	0.003
Albumin (g/L)	-0.813	-0.928 to -0.557	< 0.0001	-0.333	-0.649 to 0.081	0.1
Haemoglobin (g/dL)	-0.709	-0.852 to -0.469	< 0.0001	-0.137	-0.492 to 0.256	0.5
Endoscopic markers of disease activity						
SES-CD	0.797	0.462 to 0.933	0.0006	–	–	–
Total modified Baron score	–	–	–	0.454	-0.076 to 0.784	0.09
Radiological marker of disease activity						
MR-score	0.599	0.304 to 0.789	0.0005	0.536	0.195 to 0.761	0.004

NOTE. SES-CD: Simplified Endoscopic Activity Score for Crohn's Disease; MR-score: Magnetic-Resonance score.

^aSpearman's rho rank correlation coefficient.

Table 4. Diagnostic accuracy of serum procalcitonin ($\mu\text{g/L}$) according to ‘a priori’ defined cut-offs for disease activity in patients with Crohn’s disease

	<i>P</i> -value ^a	AUROC ^a	Standard Error ^a	ROC-defined procalcitonin cut-off ($\mu\text{g/L}$) ^a	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Crohn’s disease activity index (CDAI)								
CDAI \geq 150 (active disease)	0.007	0.741	0.0895	>0.12	48	100	100	45
CDAI \geq 300 (severe disease)	0.0001	0.963	0.0378	>0.14	100	96	88	100
C-reactive protein (mg/L)								
C-reactive protein >10 mg/L	0.0001	0.821	0.0758	>0.12	59	100	100	65
C-reactive protein >30 mg/L	0.0005	0.815	0.0898	>0.14	67	100	100	82

NOTE. AUROC: Area under the receiver operating characteristic curve; ROC: Receiver operating characteristic; **PPV: Positive predictive value;**

NPV: Negative predictive value.

^aAccording to DeLong, et al.¹⁹

Table 5. Diagnostic accuracy of serum procalcitonin level >0.05 µg/L, C-reactive protein >5 mg/L, and their combination for detecting active or severe Crohn's disease and ulcerative colitis

	CRP ^a	SPL ^b	CRP ^a and SPL ^b	CRP ^a and SPL ^b versus CRP ^a
Active Crohn's disease				P-value^c
AUROC	0.574	0.597	0.716	
Standard Error	0.102	0.101	0.0963	0.14
95% CI, AUROC	0.381 to 0.752	0.403 to 0.771	0.523 to 0.865	
Sensitivity (%)	77	82	68	
Specificity (%)	38	38	75	
PPV (%)	77	78	88	
NPV (%)	38	43	46	
Severe Crohn's disease				P-value^c
AUROC	0.674	0.652	0.783	
Standard Error	0.0508	0.0491	0.0528	0.01
95% CI, AUROC	0.479 to 0.833	0.457 to 0.816	0.595 to 0.911	
Sensitivity (%)	100	100	100	
Specificity (%)	35	30	57	
PPV (%)	32	30	41	
NPV (%)	100	100	100	
Active ulcerative colitis				P-value^c
AUROC	0.877	0.545	0.855	
Standard Error	0.103	0.0314	0.105	0.32
95% CI, AUROC	0.694 to 0.971	0.344 to 0.737	0.666 to 0.960	
Sensitivity (%)	96	9	91	
Specificity (%)	80	100	80	
PPV (%)	96	100	95	
NPV (%)	80	20	67	
Severe ulcerative colitis				P-value^c
AUROC	0.692	0.503	0.657	
Standard Error	0.0702	0.0525	0.0788	0.32
95% CI, AUROC	0.486 to 0.854	0.305 to 0.699	0.450 to 0.827	
Sensitivity (%)	100	93	93	
Specificity (%)	39	8	39	
PPV (%)	64	52	62	
NPV (%)	100	50	83	

NOTE. AUROC: Area under the receiver operating characteristic curve; CI: Confidence interval; PPV: Positive predictive value; NPV: Negative predictive value.

^aC-reactive protein >5 mg/L

^bSerum procalcitonin level >0.05 µg/L

^cComparison of AUROCs according to Delong et al.¹⁹

Table 6. Diagnostic accuracy of serum procalcitonin ($\mu\text{g/L}$) according to ‘a priori’ defined cut-offs for disease activity in patients with ulcerative colitis

	<i>P</i> -value ^a	AUROC ^a	Standard Error ^a	ROC-defined procalcitonin cut-off ($\mu\text{g/L}$) ^a	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Ulcerative colitis activity								
Active ulcerative colitis ^b	0.08	0.736	0.133	–	–	–	–	–
Severe ulcerative colitis ^c	0.2	0.648	0.111	–	–	–	–	–
C-reactive protein (mg/L)								
C-reactive protein >10 mg/L	0.003	0.774	0.093	>0.09	71	80	86	62
C-reactive protein >30 mg/L	0.008	0.773	0.103	>0.19	55	100	100	76

NOTE. AUROC: Area under the receiver operating characteristic curve; ROC: Receiver operating characteristic; **PPV: Positive predictive value;**

NPV: Negative predictive value.

^aAccording to DeLong, et al.¹⁹

^b‘Mild’, ‘moderate’ or ‘severe’ ulcerative colitis according to Truelove and Witts severity index¹³ and a SCCAI¹⁸ >5

^cAccording to Truelove and Witts severity index¹³

FIGURES LEGENDS

Figure 1. (a) Serum procalcitonin levels in patients with active or inactive inflammatory bowel disease (Patients were considered to have an active disease if they had a Crohn's disease activity index ≥ 150 or a 'mild', 'moderate' or 'severe' ulcerative colitis according to Truelove and Witts severity index with a SCCAI >5). (b) Serum procalcitonin levels in patients with C-reactive protein level >5 mg/L or ≤ 5 mg/L.

Figure 2. Correlation of serum procalcitonin level ($\mu\text{g/L}$) with C-reactive protein (mg/L) in patients with inflammatory bowel diseases.

Figure 3. Accuracy of serum procalcitonin level (SPL) >0.14 $\mu\text{g/L}$ for detecting severe Crohn's disease defined as CDAI ≥ 300 .

Figure 4. Diagnostic accuracy of serum procalcitonin level >0.05 $\mu\text{g/L}$, C-reactive protein >5 mg/L, and their combination (the SPL-CRP strategy) for detecting active or severe forms of Crohn's disease.

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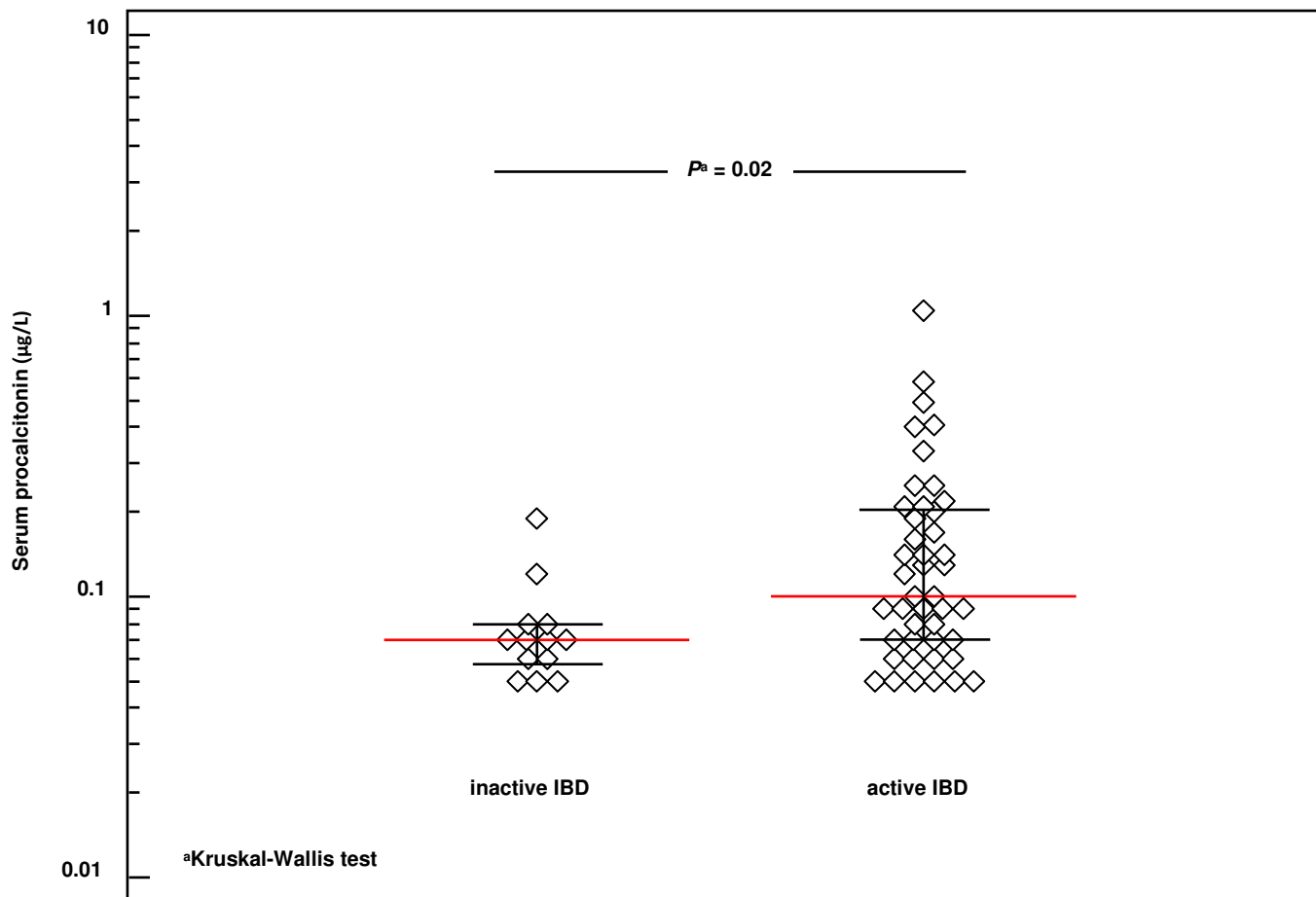


Figure 1a. Oussalah et al.

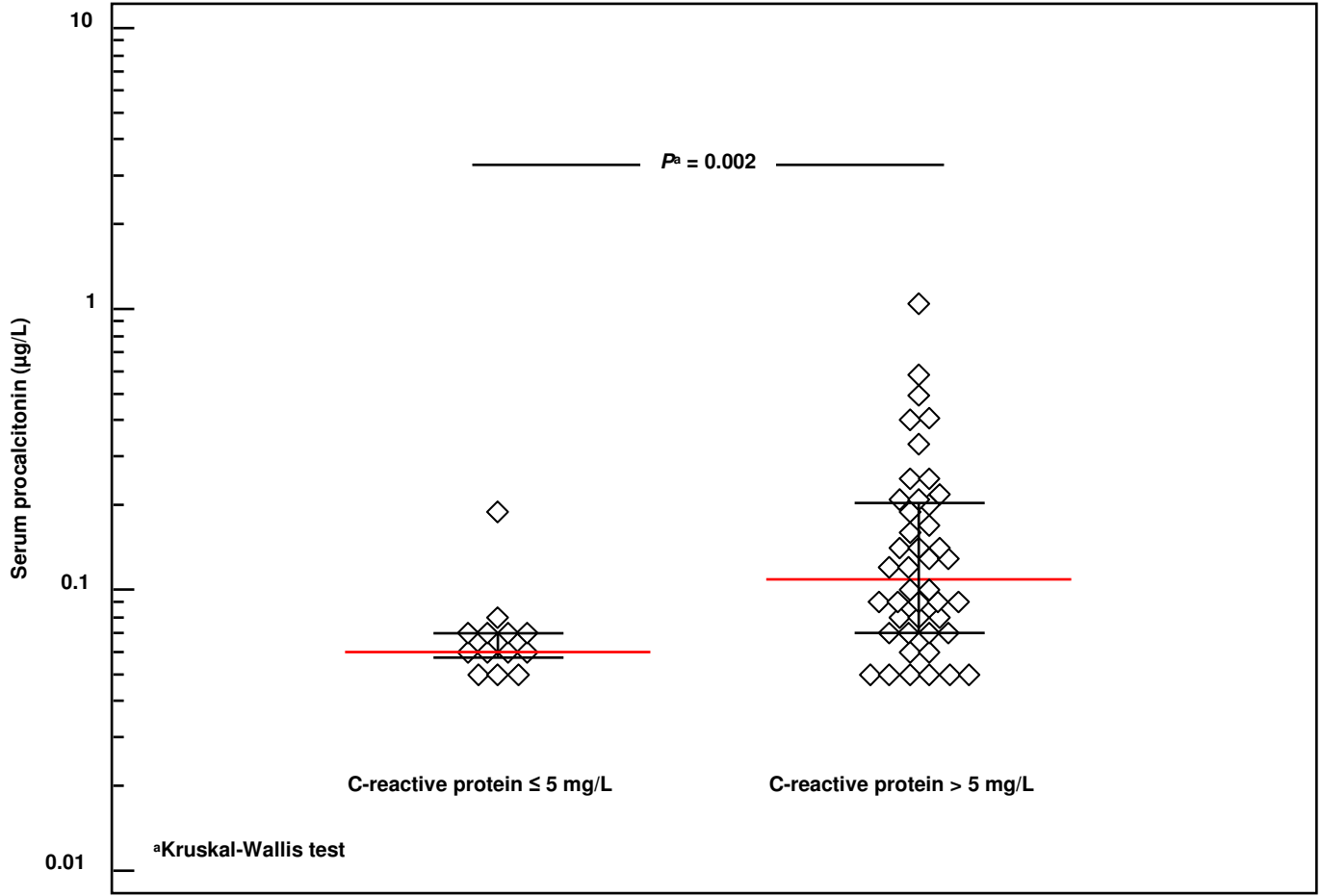


Figure 1b. Oussalah et al.

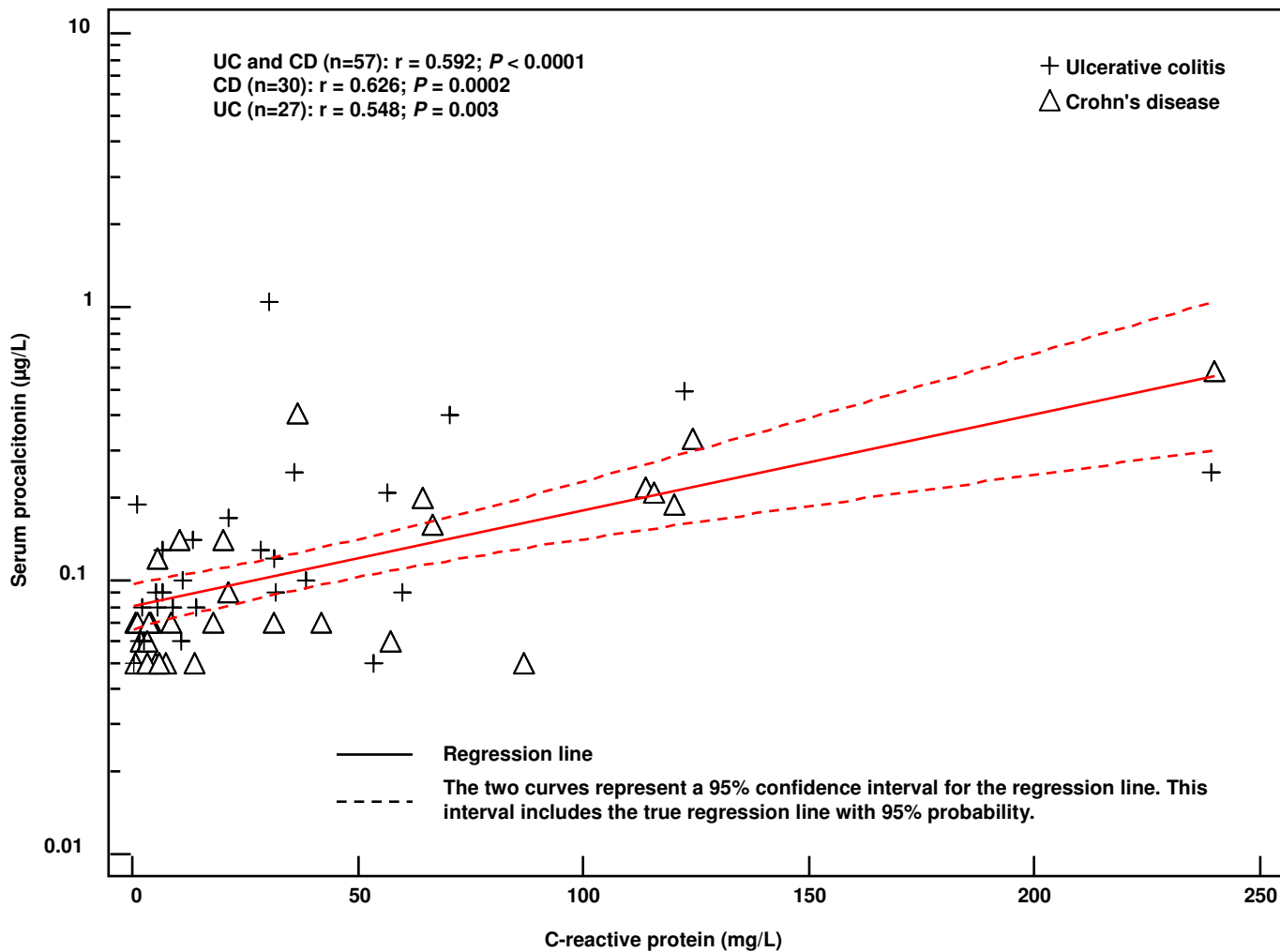


Figure 2. Oussalah et al.

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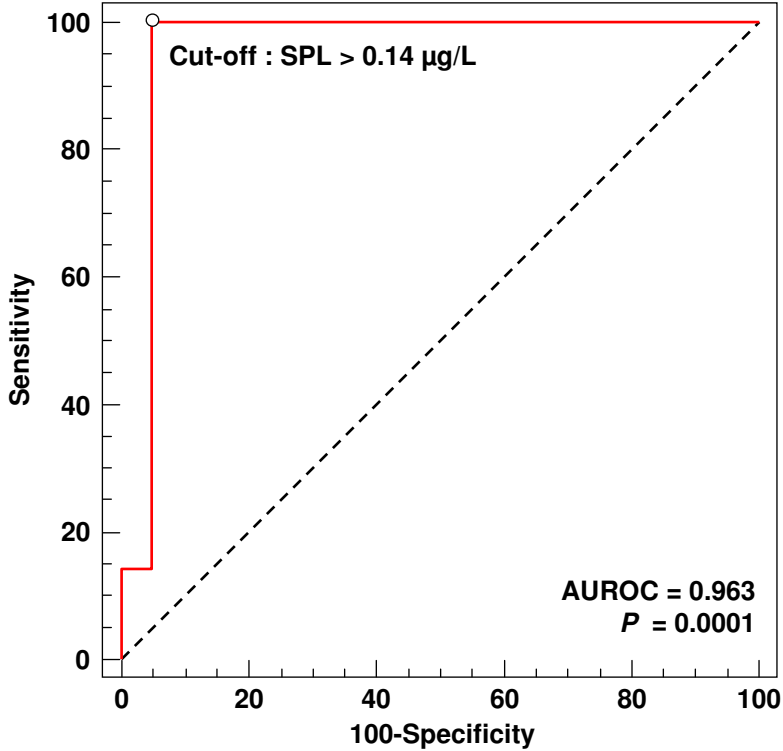


Figure 3. Oussalah et al.

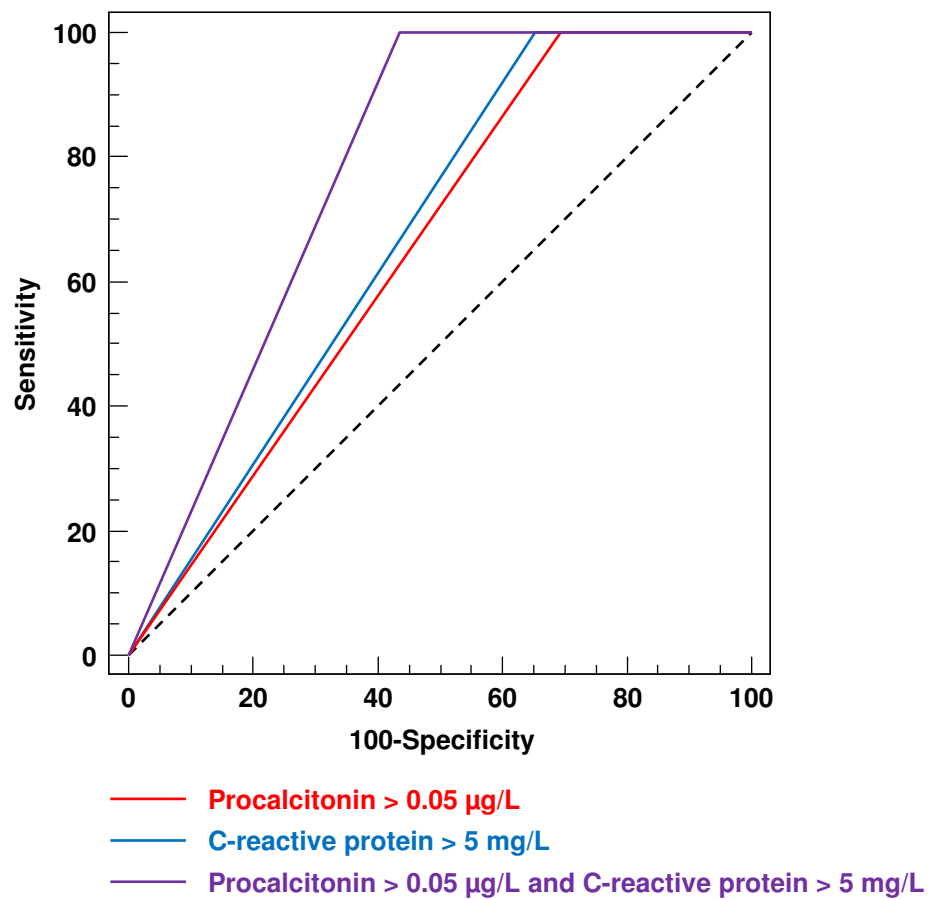


Figure 4. Oussalah et al.

Supplemental Table 1. Definition of the 6 components of the Magnetic Resonance score

Radiological item of the Magnetic resonance score	Plane	MR sequence	Definition
Diffusion-weighted imaging hyperintensity	Axial	Diffusion-weighted imaging	Presence of hyperintensity in the colonic wall segment in the DWI sequence.
Rapid gadolinium enhancement after intravenous contrast medium administration	Axial	Gradient-echo T1-weighted, arterial phase	Gadolinium enhancement in the arterial phase (20 to 25 seconds after gadolinium infusion)
Differentiation between the mucosa-submucosa complex and the muscularis propria	Axial	Single shot fast spin echo short time echo without fat saturation	Distinction in the colonic wall between two layers: 1) mucosa-submucosa complex hyperintensity; 2) muscularis propria hypointensity.
Bowel wall thickening	Axial and coronal	Gradient-echo T1-weighted, delayed phase	Thickness of the colonic wall exceeding 5 mm.
Parietal edema	Axial and coronal	Single shot fast spin echo, short time echo, without fat saturation	Thickness of the colonic wall exceeding 5 mm and hyperintensity of the mucosa-submucosa complex.
Ulceration	Axial and coronal	2D Steady-state, free precession imaging (Fast Imaging Employing Steady-state Acquisition, General Electric Company, US)	Loss of substance in the mucosa-submucosa complex.

Supplemental Table 2. Correlation between serum procalcitonin concentration ($\mu\text{g/L}$) and C-reactive protein (mg/L) in each subgroup of patients according to inflammatory bowel disease type and activity

	Active disease ^a				Inactive disease			
	Sample size	ρ^b	95% CI, ρ	<i>P</i> -value ^b	Sample size	ρ^b	95% CI, ρ	<i>P</i> -value ^b
IBD	44	0.613	0.386 to 0.770	< 0.0001	13	-0.329	-0.745 to 0.271	0.27
CD	22	0.704	0.401 to 0.868	0.0003	8	-0.378	-0.855 to 0.445	0.36
UC	22	0.514	0.118 to 0.769	0.02	5	-0.316	-0.937 to 0.785	0.60

NOTE. CI: confidence interval; IBD: Inflammatory bowel diseases; CD: Crohn's disease; UC: Ulcerative colitis.

^aActive Crohn's disease: Crohn's disease activity index ≥ 150 ; Active ulcerative colitis: 'mild', 'moderate' or 'severe' UC according to Truelove and Witts severity index¹³ and a SCCAI¹⁸ >5

^bSpearman's coefficient of rank correlation (ρ)