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

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SUMMARY

Background
Serum procalcitonin level may reflect non-infectious inflammation.

Aim
To assess the correlation of serum procalcitonin level with clinical, biological, endoscopic and radiological markers of disease activity in inflammatory bowel diseases (IBD), and to evaluate the additional diagnostic benefit of measuring serum procalcitonin level 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), serum procalcitonin level was strongly correlated with clinical, biological, endoscopic and radiological disease activity markers. In CD, the serum procalcitonin level >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 'serum procalcitonin level-CRP strategy' (CRP >5 mg/L and serum procalcitonin level >0.05 μg/L) was significantly superior to that of CRP alone for diagnosing severe CD (AUROC = 0.783 vs. 0.674; P = 0.01). In ulcerative colitis (UC) (n = 27), serum procalcitonin level was correlated with CRP and with endoscopic and radiological disease activity markers.

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

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INTRODUCTION

Procalcitonin, a prohormone of 116 amino acids is the precursor for the calcium homoeostasis 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 TNFα secretion.[2] In a study on blood of normal human volunteers, recombinant human procalcitonin had an inhibitory effect on leucocyte 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 leucocyte-derived tumour necrosis factor alpha (TNFα) secretion from isolated lymphocytes.[2] Current lines of evidence indicate that mediators such as TNFα, as well as interleukin (IL)-1b and IL-6, comprise the specific proximate stimuli to hyperprocalcitonaemia.[3, 4] TNFα 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 been 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 colitis, but found conflicting results when evaluating procalcitonin as a biological marker of disease activity.[9, 10] Only one study evaluated the diagnostic value of SPL in determining disease activity in IBD, but included a relatively small number of patients with Crohn's disease (CD), which prevents drawing conclusions.[11] Furthermore, none of the aforementioned studies evaluated the correlation of procalcitonin with endoscopic and radiological markers of IBD activity.[9–11] Finally, the additional diagnostic benefit of SPL to that of C-reactive protein (CRP) has never been evaluated in IBD.

The aims of this study was therefore to assess for the first time the correlation of SPL with clinical, biological, endoscopic and radiological markers of disease activity in patients with IBD and to evaluate the additional diagnostic benefit of measuring SPL to that of CRP in the assessment of disease activity in IBD.

MATERIALS AND METHODS

Study design

We performed an observational study of a single-centre cohort. Data were retrieved from a prospectively maintained database.

Population studied

All consecutive patients seen between 15 January 2008 and 1 June 2010 who had concomitant clinical, biological and radiological evaluation with or without concomitant colonoscopy during an IBD flare or to rule out active disease were included in the study. All investigations were prescribed at the discretion of the physician. Patients were included in the analysis if an intercurrent infection was ruled out by stool analysis for enteric pathogens and *Clostridium difficile* toxin, and quantitative real-time polymerase chain reaction in colonic biopsies for the detection of active cytomegalovirus infection in patients with severe or 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 6 January 1978 Act on data processing, data files, and individual liberties as amended by the 6 August 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 was 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 index[13] 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, haematocrit, leucocytes, 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 is measured using automated immunofluorescent assays of procalcitonin in human serum or plasma (EDTA, heparin) samples

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(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 such as rectum, sigmoid, left colon, transverse colon and right colon. The Modified Baron score was applied to each segment to obtain a segmental Modified Baron score. A total score was calculated from the sum of the segmental scores to obtain the total Modified Baron score. In patients with CD, the severity of endoscopic lesions was assessed by the Simplified Endoscopic Activity Score for Crohn's Disease (SES-CD).[16] Colonoscopy was considered concomitant to MR-DWI-colonography if it was performed within 48 h after the radiological examination, without any therapeutic intervention during this interval.

Magnetic resonance colonography

The morphological evaluation of IBD patients consisted of a magnetic resonance diffusion-weighted imaging colonography (MR-DWI-colonography) without oral or rectal preparation and with or without concomitant colonoscopy as described previously.[17] Radiological evaluation of disease activity was performed using the six-items Magnetic resonance score (MR-score).[17] The MR-score includes six radiological signs: (i) DWI hyperintensity, (ii) rapid gadolinium enhancement after intravenous contrast medium administration, (iii) differentiation between the mucosa-submucosa complex and the muscularis propria, (iv) bowel wall thickening, (v) parietal oedema and (vi) the presence of ulcer(s). The definition of each radiological sign of the MR-score is provided as supplementary material (Supplemental Table S1 online). The presence and absence of a radiological sign in a given segment were rated '1' and '0' respectively. The segmental MR-score (MR-score-S) was calculated as the sum of the numerical values obtained for the six radiological signs for a given segment. The total MR-score (MR-score-T) was calculated as the sum of the MR-score-S in a patient, with values ranging from 0 to 30 in the case of UC and from 0 to 36 in the case of CD.

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 (nonstricturing, nonpenetrating)	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)*		
Mesalazine (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
Haematocrit (g/dL)	35.8	5.5
Platelets ($\times 10^9$/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†	213	138
SES-CD‡ (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
Leucocytes ($\times 10^9$/L)	9.510	7.720 to 12.030
Magnetic-resonance score (0–36)§	10	6 to 15

IBD, inflammatory bowel diseases; SES-CD, simplified endoscopic activity score for Crohn's disease; IQR, interquartile range 25–75th percentile.

* A patient may receive more than one concomitant medication. † Clinical evaluation of disease activity. ‡ Endoscopic evaluation of disease activity. § Radiological 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)*		
Mesalazine	10	37
Oral or intravenous corticosteroids	10	37
Azathioprine	7	26
Methotrexate	0	-
Ciclosporin	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
Haematocrit (g/dL)	34.0	5.9
Leucocytes ($\times 10^9$/L)	9.200	3.708
Platelets ($\times 10^9$/L)	430	151
Albumin (g/L) (n = 24)	32.3	8.0
Simple clinical colitis activity index†	7	4
Total modified Baron score‡ (n = 15)	8	5
Magnetic-Resonance score (0–30)§	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

IBD, inflammatory bowel diseases; IQR, interquartile range 25–75th percentile.

* A patient may receive more than one concomitant medication.

† Clinical evaluation of disease activity.

‡ Endoscopic evaluation of disease activity.

§ Radiological evaluation of disease activity.

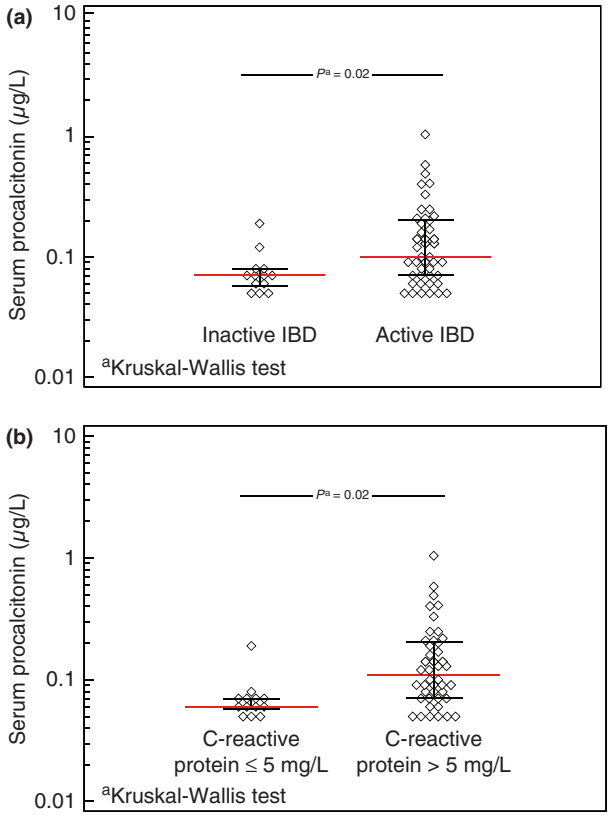

Figure 1 | (a) Serum procalcitonin levels in patients with active or inactive inflammatory bowel disease (Patients were considered to have an active disease if they had a Crohn's disease activity index ≥150 or a 'mild', 'moderate' or 'severe' ulcerative colitis according to Truelove and Witts severity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

Definition of active disease and severe disease

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 index,[13] and a SCCAI >5.[18] Patients were considered to have severe disease if they had 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

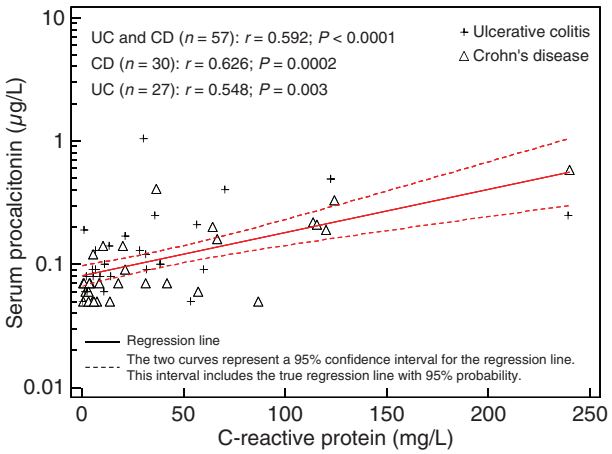

Figure 2 | Correlation of serum procalcitonin level (μg/L) with C-reactive protein (mg/L) in patients with inflammatory bowel diseases.

coefficients. The diagnostic accuracy of serum procalcitonin (μg/L) for detecting severe forms of IBD was evaluated using receiver operating characteristic (ROC) analysis according to DeLong *et al.*[19] 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 15 January 2008 and 1 June 2010, 57 patients with a diagnosis of IBD underwent clinical, biological, endoscopic, histological and/or radiological 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 with 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

Table 3 | Correlation of serum procalcitonin concentration (μg/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)		
	rho*	95% CI	*P*-value*	rho*	95% CI	*P*-value*
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

SES-CD, simplified endoscopic activity score for Crohn's disease; MR-score, magnetic-resonance score.

* Spearman's rho rank correlation coefficient.

Table 4 | Diagnostic accuracy of serum procalcitonin (μg/L) according to '*a priori*' defined cut-offs for disease activity in patients with Crohn's disease

	P-value*	AUROC*	Standard error*	ROC-defined procalcitonin cut-off (μg/L)*	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Crohn's disease activity index (CDAI)								
CDAI ≥150 (active disease)	0.007	0.741	0.0895	>0.12	48	100	100	45
CDAI ≥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

AUROC, area under the receiver operating characteristic curve; ROC, receiver operating characteristic; PPV, positive predictive value; NPV, negative predictive value.

* According to DeLong, *et al.*[19]

≤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. Serum procalcitonin level 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 leucocytes (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 S2 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 (Supporting Information Table S2).

Diagnostic accuracy of serum procalcitonin for detecting disease activity. In patients with CD, using ROC analysis, an SPL >0.14 μg/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), 0.822–0.999; P = 0.0001] (Table 4 and Figure 3). In CD patients, SPL >0.14 μg/L had a sensitivity of 67%, a specificity of 100%, and an AUROC of 0.815 (95% CI, 0.631–0.932; P = 0.0005) for detecting patients with a CRP >30 mg/L (Table 4). Consistently, the median SPL was significantly higher in patients with a CDAI ≥300 (0.21 μg/L; IQR 25–75th, 0.19–0.30) compared with those with a CDAI <300 (0.07 μg/L; IQR 25–75th, 0.05–0.07) (P = 0.0002).

In comparison with a CRP cut-off of 5 mg/L, an SPL cut-off of 0.05 μg/L had the same diagnostic accuracy

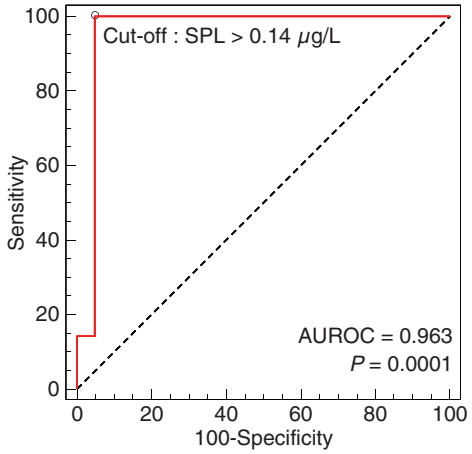

Figure 3 | Accuracy of serum procalcitonin level (SPL) >0.14 μg/L for detecting severe Crohn's disease defined as CDAI ≥300.

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

AUROC, area under the receiver operating characteristic curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.

* C-reactive protein >5 mg/L.

† Serum procalcitonin level >0.05 μg/L.

‡ Comparison of AUROCs according to DeLong *et al.*[19]

(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 an SPL cut-off of 0.05 μg/L, called the 'SPL-CRP strategy', yielded a better specificity for diagnosing active or severe CD (Table 5). Moreover, the diagnostic accuracy of the SPL-CRP strategy was

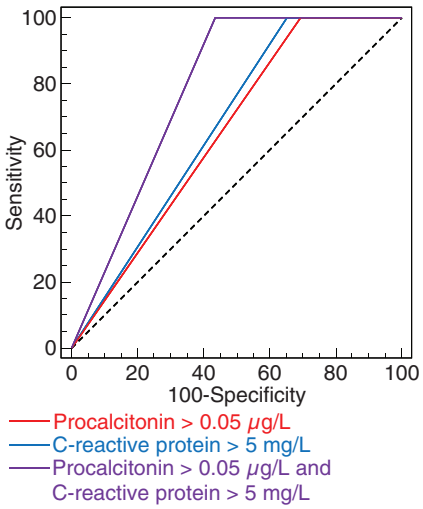

Figure 4 | Diagnostic accuracy of serum procalcitonin level >0.05 μg/L, C-reactive protein >5 mg/L and their combination (the SPL-CRP strategy) for detecting active or severe forms of Crohn's disease.

significantly superior to that of CRP alone for diagnosing severe CD with an AUROC of 0.783 vs. 0.674 ($P = 0.01$) (Table 5 and Figure 4).

Ulcerative colitis

Correlation of serum procalcitonin level with clinical, biological, endoscopic and radiological markers of activity. In patients with UC ($n = 27$), SPL was correlated with the SCCAI ($r = 0.423$, $P = 0.03$), CRP level ($r = 0.548$, $P = 0.003$) and MR-score ($r = 0.536$, $P = 0.004$). In contrast, SPL was not correlated with albumin, haemoglobin and the total modified Baron score (Table 3). SPL was significantly correlated with CRP in patients with active UC as opposed to patients with inactive UC (Supporting Information Table S2).

Diagnostic accuracy of serum procalcitonin for detecting disease activity. In patients with UC, ROC analysis did not reveal any significant threshold of SPL for the detection of active or severe disease ($P = 0.08$ and $P = 0.2$ respectively) (Table 6). The SPL-CRP strategy did not yield a better accuracy for diagnosing active or severe UC in comparison with CRP alone (Table 5).

DISCUSSION

This is the first study showing that SPL is correlated with clinical, biological, endoscopic and/or radiological disease activity in patients with IBD. To date, three studies have evaluated procalcitonin in IBD.[9–11] By pooling UC and CD patients, we found that SPL was significantly higher in patients with active IBD. These results are consistent with those of a previously reported study.[9] Consistently, by pooling UC and CD patients, SPL was significantly higher in patients with a CRP >5 mg/L and was correlated with CRP levels. This finding is also consistent with that in the study by Oruc *et al.* that demonstrated a significant correlation between SPL and CRP in patients with IBD.[11]

When considering only patients with CD, Herrlinger *et al.* demonstrated that SPL was significantly correlated

Table 6 | Diagnostic accuracy of serum procalcitonin (μg/L) according to '*a priori*' defined cut-offs for disease activity in patients with ulcerative colitis

	P-value*	AUROC*	Standard error*	ROC-defined procalcitonin cut-off (μg/L)*	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Ulcerative colitis activity								
Active ulcerative colitis†	0.08	0.736	0.133	–	–	–	–	–
Severe ulcerative colitis‡	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

AUROC, area under the receiver operating characteristic curve; ROC, receiver operating characteristic; PPV, positive predictive value; NPV, negative predictive value.

* According to DeLong, *et al.*[19].

† 'Mild', 'moderate' or 'severe' ulcerative colitis according to Truelove and Witts severity index[13] and a SCCAI[18] >5.

‡ According to Truelove and Witts severity index[13].

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with the CDAI, while no correlation was found with CRP level.[9] In contrast, in the study by Thia *et al.*, SPL showed no correlation with CD activity using the Harvey-Bradshaw index (HBI).[10] This discrepancy may be partly explained by the fact that CD activity has been scored with the HBI in the study by Thia *et al.*,[10] in contrast to our study and that of Herrlinger *et al.*[9] that used the CDAI as CD activity score. In the study by Oruc *et al.*, SPL was not correlated with CDAI.[11] However, this study included only nine CD patients, which prevents any conclusion. It is noteworthy that none of the three studies[9–11] had evaluated endoscopic or radiological markers of disease activity.

Our study showed that in patients with UC, SPL was correlated with the SCCAI, CRP and the MR-score score, whereas no correlation was found with endoscopic disease activity scores. Among the three studies that evaluated SPL in IBD patients,[9–11] only one has specifically evaluated the SPL in the subgroup of patients with UC, and did not show any correlation between SPL and clinical disease activity.[10] This difference may be partly explained by the fact that UC activity has been scored with the Physician Global Assessment[20] in the study by Thia *et al.*,[10] in contrast to our study that used the SCCAI, which is a well validated disease activity index for UC.[21, 22]

In the study by Oruc *et al.* a procalcitonin cut-off value of 0.05 μg/L, found in ROC analysis, had a poor accuracy (sensitivity, 67%; specificity 42%) for detecting active IBD as defined by a CDAI >150, or a 'moderate' or 'severe' UC according to Truelove and Witts severity index.[13] Importantly, by using ROC analysis, we were able to identify an SPL cut-off of 0.14 μg/L as having a high accuracy (sensitivity, 100%; specificity, 95%) for detecting severe forms of CD as defined by a CDAI ≥300. Interestingly, by adding SPL measurement to routine CRP evaluation (The SPL-CRP strategy), we were able to double the specificity of the SPL-CRP strategy for diagnosing active or severe forms of CD when compared with a 'CRP alone'-based strategy.

Overall, we found that the performance of procalcitonin for evaluating disease activity was weaker in UC compared with CD. Consistently, there was no cut-off value for SPL capable of detecting severe forms of UC in our study. This is consistent with previous reports.[9, 10]

From a mechanistic point of view, one can speculate that the best correlation of procalcitonin with the degree of activity of CD is linked to the fact that TNFα plays a central role in the pathogenesis of this disease.

In conclusion, our results indicate that procalcitonin might be useful in clinical practice to assess disease activity in patients with CD. Notably, we demonstrated for the first time that SPL was correlated with endoscopic and radiological markers of activity in CD, and with radiological activity in UC. In patients with CD, a threshold of 0.14 μg/L for procalcitonin may detect the most severe forms of the disease. The combination of procalcitonin with CRP would be more efficient than CRP alone for the diagnosis of active or severe CD. Our results need to be confirmed in independent studies.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Definition of the six components of the magnetic resonance score.

Table S2. Correlation between serum procalcitonin concentration (μg/L) and C-reactive protein (mg/L) in each subgroup of patients according to inflammatory bowel disease type and activity.

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