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Alimentary Tract

Deep ulcers are associated with increased C-reactive protein in active ulcerative colitis

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ABSTRACT

Background: Increased C-reactive protein (CRP) is used to diagnose and predict response to treatment in acute severe ulcerative colitis (UC).
Aims: To investigate the connection between CRP elevation and deep ulcers in UC.
Methods: Patients with active UC were enrolled in a multicenter prospective cohort and a retrospective cohort of consecutive patients undergoing colectomy from 2012 to 2019.
Results: Forty-one (9 (22%) with deep ulcers) patients were included in the prospective cohort: 4/5 (80%) patients with CRP > 100 mg/L, 2/10 (20%) patients with CRP between 30 and 100 mg/L and 3/26 (12%) patients with CRP < 30 mg/L had deep ulcers ($p = 0.006$). In the retrospective cohort [46 patients (31 (67%) with deep ulcers)], 14/14 (100%) patients with CRP > 100 mg/L, 11/17 (65%) patients with CRP between 30 and 100 mg/l and 6/15 (40%) patients with CRP < 30 mg/L had deep ulcers ($p = 0.001$). Positive predictive value of CRP > 100 mg/l for presence of deep ulcers was 80% and 100% in both cohorts, respectively.
Conclusions: CRP elevation is a robust surrogate marker for presence of deep ulcers in UC. Elevated CRP or presence of deep ulcers could influence the choice of medical therapy in acute severe UC.

1. Introduction

Ulcerative colitis (UC) is a chronic disease characterized by acute episodes of bloody diarrhea with varying degrees of severity. The most feared event, acute severe UC, can lead to life-threatening and systemic complications [1]. The Truelove and Witts criteria are used for rapid identification of those patients with acute severe UC requiring hospital admission and intensive treatment [2]. Historically, systemic inflammation was evaluated by the erythrocyte sedimentation rate (ESR) [3]. The European Crohn's and Colitis (ECCO) guidelines suggested to replace ESR by C-reactive protein (CRP). Compared to what is described in Crohn's disease, CRP elevation has been shown to be preferentially associated with severe clinical activity in UC [4]. Next to biomarkers, a flexible sigmoidoscopy is recommended to assess disease severity in UC [2]. In retrospective series of patients admitted for an acute severe UC episode, presence of deep ulcers of the colorectal mucosa was associated with treatment failure and colectomy [5–7]. However, these results may also reflect a circular argument if decision of colectomy was based on endoscopic findings [8]. Moreover, most research on severe lesions in acute UC was conducted before the implementation of bio-

Abbreviations: CRP, C-reactive protein; CI, Confidence Interval; IQR, interquartile range; UC, ulcerative colitis.

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logical therapies in routine clinical practice, dramatic improvement of endoscopy and wide use of the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) [9]. It has also been shown that high fecal calprotectin levels at admission was associated with lower probability of response to medical therapy [10]. Overall, the relationship between systemic inflammation and severity of colorectal lesions has not been thoroughly investigated in acute UC. These factors point out that deep ulcers may be an overlooked topic in acute UC.

The objective of the present study was to describe in-depth the relationship between systemic inflammation, measured by CRP elevation and, low albumin and hemoglobin levels, and deep ulcers in acute UC.

2. Methods

2.1. Design

We performed a study combining data from an international multicenter prospective cohort of patients with acute UC and from a single-center retrospective cohort of patients undergoing colectomy for acute UC.

2.2. Objectives

The primary objective of this study was to compare the proportion of patients with deep ulcers according to prespecified CRP thresholds. Patients were divided into three groups according to their CRP serum levels as described below. Two thresholds of CRP were selected: 30 mg/L that corresponds to the cut-off defining acute severe UC in the ECCO guidelines [2] and 100 mg/L recently shown to be associated with non-response to steroids in acute severe UC [11].

Secondary objectives were to *i)* compare the proportion of deep ulcers according to albumin levels in patients with active UC; *ii)* compare the proportion of deep ulcers according to CRP/albumin ratio in patients with active UC; *iii)* compare the proportion of deep ulcers according to hemoglobin levels in patients with active UC; *iv)* investigate the correlation between CRP, albumin and hemoglobin in patients with active UC.

Albumin was considered as low if < 35 g/L [12]. Hemoglobin was considered as low if < 10.5 g/dL[2]. Based on literature review, a cut-off of 0.32 was selected for CRP/albumin ratio predicting avoidance of colectomy at 12 months in a retrospective multicentric cohort of acute severe UC patients [13].

2.3. Prospective cohort: selection criteria

Consecutive adult patients admitted for acute severe UC from May 2020 to May 2021 in Bordeaux University Hospitals (Bordeaux, France), Beaujon University Hospitals (Paris, France) and McGill University Health centre (Montréal, Canada) were included prospectively in an observational prospective cohort. Acute severe UC was defined according to the Truelove and Witts criteria: six or more bloody daily stools and at least one of the following: fever (temperature > 38.5 °C), tachycardia (> 90/min), anemia (hemoglobin less than 10.5 g/dL) or CRP > 30 mg/L[2]. In parallel, a control group of patients with non-severe active UC was enrolled, defined as disease activity symptoms corresponding to a partial Mayo score ≥ 4 with a rectal bleeding subscore ≥ 1 without Truelove and Witts criteria. Patients with features of Crohn's disease (perianal lesions, ileal lesions or suggestive endoscopic lesions) were excluded. The cohort was observational only and therapeutic management was not standardized.

2.4. Retrospective cohort: selection criteria

An additional retrospective cohort was constituted by consecutive patients > 15 years old who underwent colectomy for active UC in a single tertiary care center (Bordeaux University Hospitals) from January 2012 to February 2019. Patients were excluded in case of colectomy for dysplasia or cancer, segmental colectomy, Crohn's disease diagnosed on the surgical specimen. Patients without an endoscopy within three months before surgery were removed from the analysis. Enrolment date corresponded to the date of colectomy. For acute severe UC patients and non-severe active UC patients treated by corticosteroids, a staged colectomy was performed as recommended by ECCO guidelines. At time of colectomy, rectum and distal sigmoid were left in place and anchored to the abdominal wall and a terminal ileostomy was created [14].

2.5. Assessment of deep ulcers

In the prospective cohort, endoscopic activity was evaluated by flexible sigmoidoscopy or total colonoscopy at enrolment. Deep ulcers were defined as an erosion/ulcer subscore of 3 in the UCEIS score corresponding to presence of deep ulcerations [9].

In the retrospective cohort, deep ulcers were assessed by examination of the surgical specimen and the last endoscopic examination before colectomy that was scored based on reports, pictures or videos when available. Two IBD-specialized pathologists (AR and MM) blinded from the original pathology report and patient outcomes reviewed the slides for presence and grading of ulcers on each surgical specimen. In case of disagreement, a third revision was performed by one of the two pathologists (AR). An average number of ten histologic blocks from the whole colectomy specimen were done and slides were examined following hematoxylin-eosin staining. Deep ulcers were defined as at least one ulcer reaching the circular muscle layer in the worst lesions of the retrospective specimen. In case of subtotal colectomy, patients without deep ulcers on surgical specimens but having deep endoscopic ulcers located in the rectum or the lower sigmoid were assigned to the deep ulcers group.

2.6. Biomarkers

In the prospective cohort, hemoglobin, CRP and albumin were measured on the same day than endoscopy. In the retrospective cohort, albumin (last measurement before albumin infusion or parenteral nutrition initiation), CRP and hemoglobin (last measurement before blood transfusion) were retrieved from electronic health records. In case of multiple measurements of one of the biomarkers, the latest taken before colectomy was retained.

2.7. Statistical analyses

Continuous data and categorical variables were expressed as median (interquartile range [IQR]) and frequencies, respectively, and compared using a Student's *t*-test and a chi-square test, respectively. Receiver operating characteristic (ROC) curves were plotted using sensitivity against (1-Specificity). Correlation of continuous variables was evaluated using Spearman method. Two-sided statistical tests were used for all analyses. A p-value <0.05 was considered as significant. For controlling false discovery rate related to multiple testing, we report p-values for the primary objective of the study only. Statistical analyses were performed using R version 3.5.1 (R Development Core Team, Vienna, Austria).

2.8. Ethical considerations

This study was conducted in accord with the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (2014),

Table 1
Characteristics of the patients enrolled in the two cohorts.

Variable	Prospective cohort $n = 41$	Retrospective cohort $n = 46$
Age in years, median (IQR)	42 (34, 57)	39 (23, 57)
Body mass index, kg/m2, median (IQR)	24.5 (21.8, 28.8)	21.4 (19.2, 23.8)
Disease duration, years, median (IQR)	5.3 (1.7, 11.3)	1.9 (0.3, 6.0)
Disease extent, n (%)		
- Pancolitis	21 (51)	37 (82)
- Left-sided colitis	15 (37)	8 (18)
- Proctitis	5 (12)	0 (0)
Presence of Truelove-Witts criteria, n (%)	19 (46)	41 (89)
Lichtiger score at enrolment, median (IQR)	11 (7, 13)	11 (10, 14)
Never exposed to biological therapy, n (%)	27 (66)	22 (48)
Steroids for current flare, n (%)	16 (39)	33 (72)
C- Reactive protein, mg/L, median (IQR)	11.7 (4.0, 57.7)	57.7 (14.7, 120.8)
Hæmoglobin, g/dL, median (IQR)	12.9 (10.4, 13.7)	10.1 (8.9, 11.5)
Albumin, g/L, median (IQR)	33.8 (26.4, 38.9)	28.6 (24.9, 31.9)
Surgery performed for current flare, n (%)	6 (15)	46 (100)

IQR: Interquartile range.

as well as in respect of the requirements set out in the applicable standard operation procedures of the participating centers. The study was approved by the *Comité de Protection des Personnes Ouest IV - Nantes* (Reference 69/19–2, 19.09.19.61935).

3. Results

3.1. Study population: prospective cohort

After exclusion of two patients with features of Crohn's disease, 41 patients [median (IQR) age 42 years (34, 57)] were included in the prospective cohort: 19 (46%) patients having an acute severe UC and 22 (54%) a non-severe active UC. Twenty-seven (66%) had never been exposed to biologics at admission. Median (IQR) CRP, albumin and hemoglobin levels at inclusion were 59 (38, 95) mg/L, 26.2 (23.4, 30.8) g/L and 10.3 (9.2, 11.6) g/dL in patients having active severe UC and 4 (3, 8) mg/L ($p<0.01$), 38.6 (35.1, 41.0) g/L ($p<0.01$) and 13.6 (13.1, 14.6) g/dL ($p<0.01$) in those with non-severe active UC, respectively.

At enrolment, all patients were evaluated by endoscopy: median UCEIS score was 5 (4, 6). Nine (22%) patients displayed deep ulcers, all included in the acute severe UC group.

3.2. Study population: retrospective cohort

Among the 50 patients who underwent colectomy for active UC during the study period, 46 [median (IQR) age 39 years (23, 57)] were analyzed after removing four patients without an endoscopic assessment performed within the three months before colectomy. Twenty-two (48%) patients had never been exposed to biologics at admission. Five (11%) patients were operated for non-severe refractory UC and 41 (89%) for acute severe UC. A staged colectomy with temporary ileostomy was performed in 44 (94%) patients.

The endoscopic assessment was performed 7 (4, 12) days before colectomy with a median UCEIS score of 6 (5, 7). Twenty-three (50%) patients had deep ulcers on the surgical specimen. From the 23 (50%) patients without deep ulcers on the surgical specimen, 8 had deep ulcers located in the rectum and/or the sigmoid at endoscopy and were also considered having deep ulcers. Overall, 31 (67%) patients had deep ulcers in the retrospective cohort.

Characteristics of patients enrolled in the two cohorts are described in Table 1.

3.3. Association between CRP and deep ulcers

In the prospective cohort, patients' characteristics at enrolment were similar between patients with CRP > 100 mg/L, CRP 30–100 mg/L or CRP < 30 mg/L especially for previous exposure to biologics ($p = 0.11$) or disease duration ($p = 0.40$) (Table 2). Four out of five (80%) patients with CRP > 100 mg/l, 2/10 (20%) patients with CRP between 30 and 100 mg/l and 3/26 (12%) patients with CRP < 30 mg/l had deep ulcers ($p = 0.006$) (Fig. 1A). In the retrospective cohort, 14/14 (100%) patients with CRP > 100 mg/l, 11/17 (65%) of patients with CRP between 30 and 100 mg/l and 6/15 (40%) of patients with CRP < 30 mg/l had deep ulcers ($p = 0.001$) (Fig. 1B).

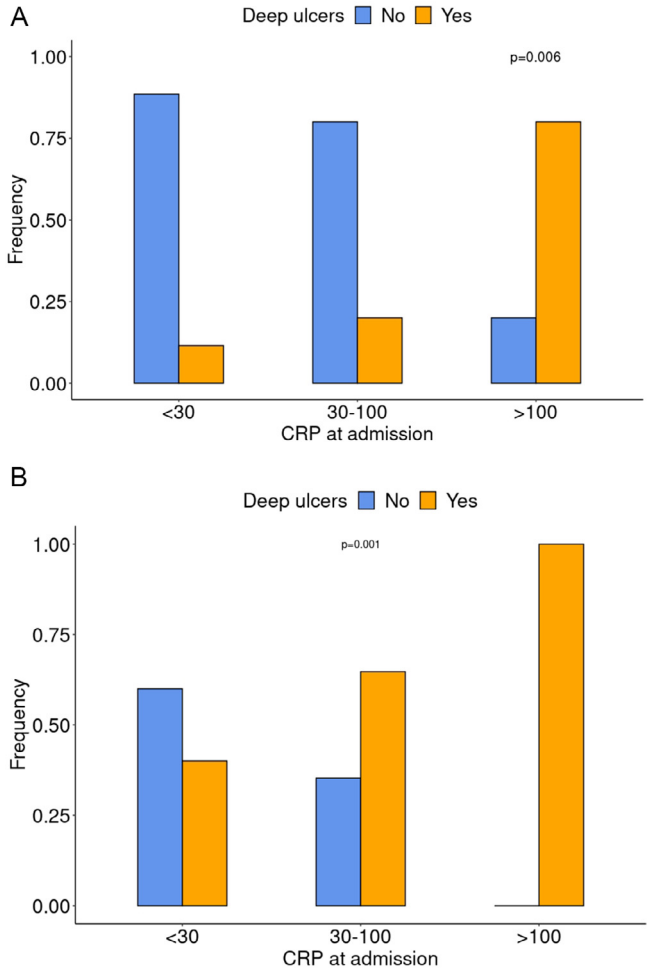

Fig. 1. A. Frequency of deep ulcers in the prospective cohort according to CRP levels. B. Frequency of deep ulcers in the retrospective cohort according to CRP levels.

Table 2
Characteristics of the patients in the prospective cohort according to the CRP levels.

Variable	CRP < 30 mg/l, $n = 26$	30 ≤ CRP ≤ 100 mg/l, $n = 10$	CRP > 100 mg/l, $n = 5$	p-value
UCEIS ulcer = 3, n (%)	3 (12)	2 (20)	4 (80)	< 0.01
Body mass index, kg/m2, median (IQR)	24.8 (21.6, 29.0)	23.1 (22.3, 26.0)	23.8 (21.8, 24.6)	0.80
Disease duration, years, median (IQR)	5.3 (1.3, 8?1)	7.9 (4.0, 16.9)	1.7 (1.4, 17.3)	0.40
Disease extent, n (%)				0.50
- Pancolitis	10 (38)	3 (30)	2 (40)	
- Left-sided colitis	11 (42)	7 (70)	3 (60)	
- Proctitis	5 (19)	0 (0)	0 (0)	
Lichtiger score at enrolment, median (IQR)	8.5 (6.0, 11.8)	13.0 (13.0, 14.0)	13.0 (12.0, 13.0)	< 0.01
Never exposed to biological therapy, n (%)	20 (77)	4 (40)	3 (60)	0.11
Hæmoglobin, g/dL, median (IQR)	13.6 (12.5, 14.6)	11.1 (9.3, 11.7)	10.2 (9.2, 12.9)	< 0.01
Albumin, g/L, median (IQR)	36.2 (33.9, 41.0)	27.9 (25.6, 31.8)	21.9 (19.9, 23.9)	< 0.01
Surgery performed for current flare, n (%)	1 (4)	3 (30)	2 (40)	0.03

CRP: C-reactive protein.

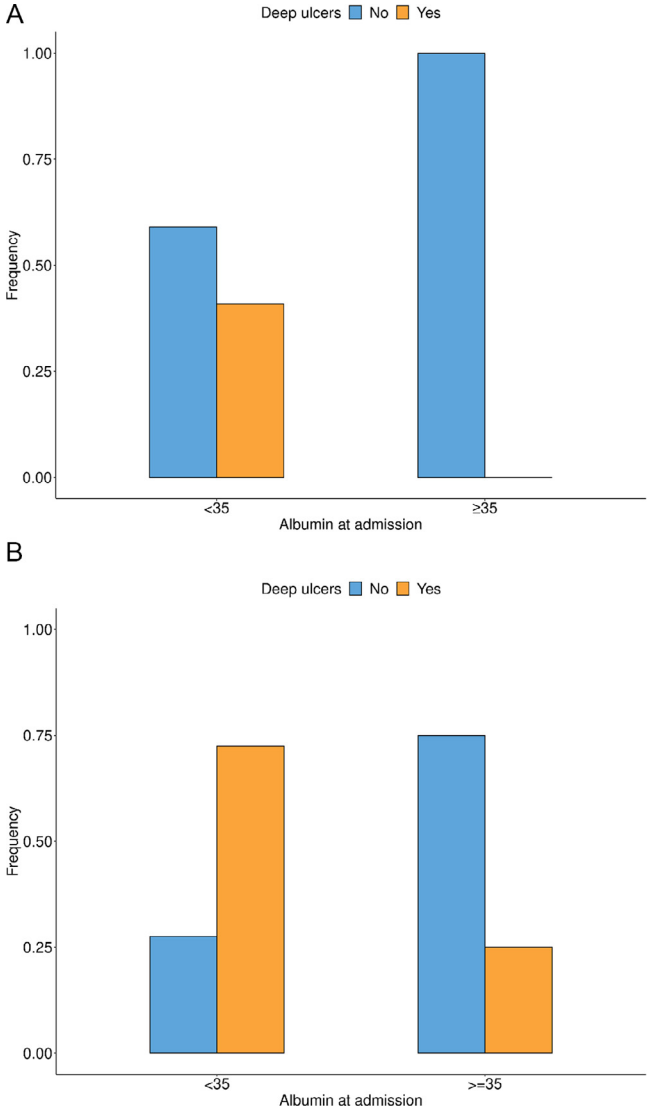

Fig. 2. A. Frequency of deep ulcers in the prospective cohort according to albumin levels. B. Frequency of deep ulcers in the retrospective cohort according to albumin levels.

3.4. Association between albumin levels and deep ulcers

In the prospective cohort, 9/22 (40%) of patients with albumin < 35 g/L and 0/16 (0%) patients with albumin ≥ 35 g/L had deep ulcers (Fig. 2A). In the retrospective cohort, 29/40 (73%) of patients with albumin < 35 g/L and 1/4 (25%) patients with albumin ≥ 35 g/L had deep ulcers (Fig. 2B).

3.5. Association between CRP/albumin ratio and deep ulcers

In the prospective cohort, 9/20 (40%) of patients with CRP/albumin ratio > 0.32 and 0/18 (0%) patients with CRP/albumin ratio ≤ 0.32 had deep ulcers. In the retrospective cohort, 25/34 (74%) of patients with CRP/albumin ratio > 0.32 and 5/9 (55%) patients with CRP/albumin ratio ≤ 0.32 had deep ulcers.

3.6. Association between hemoglobin and deep ulcers

In the prospective cohort, 7/11 (63%) of patients with hemoglobin < 10.5 g/dL and 2/30 (6%) patients with hemoglobin ≥ 10.5 g/dL had deep ulcers. In the retrospective cohort, 20/26 (77%) of patients with hemoglobin < 10.5 g/dL and 11/21 (52%) patients with hemoglobin ≥ 10.5 g/dL had deep ulcers.

ROC curves for CRP, albumin, CRP/albumin ratio and hemoglobin to predict presence of deep ulcers in the two cohorts are displayed in Fig. 3. Sensitivity, specificity, positive and negative predictive values for each parameter regarding presence of deep ulcers are presented in Table 3. Table 4 displays area under the curve (AUC) for each parameter in the two cohorts.

3.7. Correlation between CRP levels and biological and endoscopic scores

In the prospective cohort, CRP levels were correlated with albumin levels (Spearman coefficient −0.65, $p < 0.001$), hemoglobin levels (Spearman coefficient −0.62, $p < 0.001$) and total UCEIS score (Spearman coefficient 0.57, $p < 0.001$).

In the retrospective cohort, CRP levels were correlated with albumin levels (Spearman coefficient −0.35, $p = 0.02$). No correlation was observed between CRP and hemoglobin levels (Spearman coefficient −0.20, $p = 0.17$) and CRP and total UCEIS score (Spearman coefficient −0.07, $p = 0.70$).

4. Discussion

Evaluation of disease severity is the prime concern in acute UC to prevent morbidity and mortality related to acute severe UC complications [2]. Biomarkers such as CRP and albumin have received most attention in the last years. Using data from an international prospective cohort of well-phenotyped patients with active UC, we found a robust association between CRP elevation, low levels of albumin and hemoglobin and presence of deep ulcers. Positive predictive value for presence of deep ulcers in patients with CRP > 100 mg/L reached 100% in the retrospective cohort. We confirmed these findings in a retrospective analysis of colectomy specimens of patients with active UC.

Table 3
Performance of CRP, albumin, CRP/albumin ratio and hemoglobin to predict the presence of deep ulcers in the two cohorts.

	Prospective cohort (n = 41)	Retrospective cohort (n = 46)
CRP > 100 mg/L		
Sensitivity	44 (14–79)	45 (27–64)
Specificity	97 (84–100)	100 (78–100)
Positive predictive value	80 (28–99)	100 (77–100)
Negative predictive value	57 (32–100)	47 (29–65)
Albumin < 35 g/l		
Sensitivity	100 (66–100)	97 (83–100)
Specificity	55 (36–74),	21 (5–51)
Positive predictive value	41 (21–64)	72 (56–85)
Negative predictive value	100 (79–100)	75 (19–99)
CRP/albumin ratio ≤ 0.32		
Sensitivity	100 (66–100)	83 (65–94)
Specificity	62 (42–79)	31 (9–61),
Positive predictive value	45 (23–68)	74 (56–87)
negative predictive value	100 (81–100)	44 (14–79)
hemoglobin < 10.5 g/dl		
Sensitivity	78 (40–97)	65 (45–81)
Specificity	88 (71–96)	62 (35–85)
Positive predictive value	64 (31–89)	77 (56–91)
Negative predictive value	25 (7–87)	48 (26–70)

Results are presented as percentages (95% Confidence Interval). CRP: C-reactive protein.

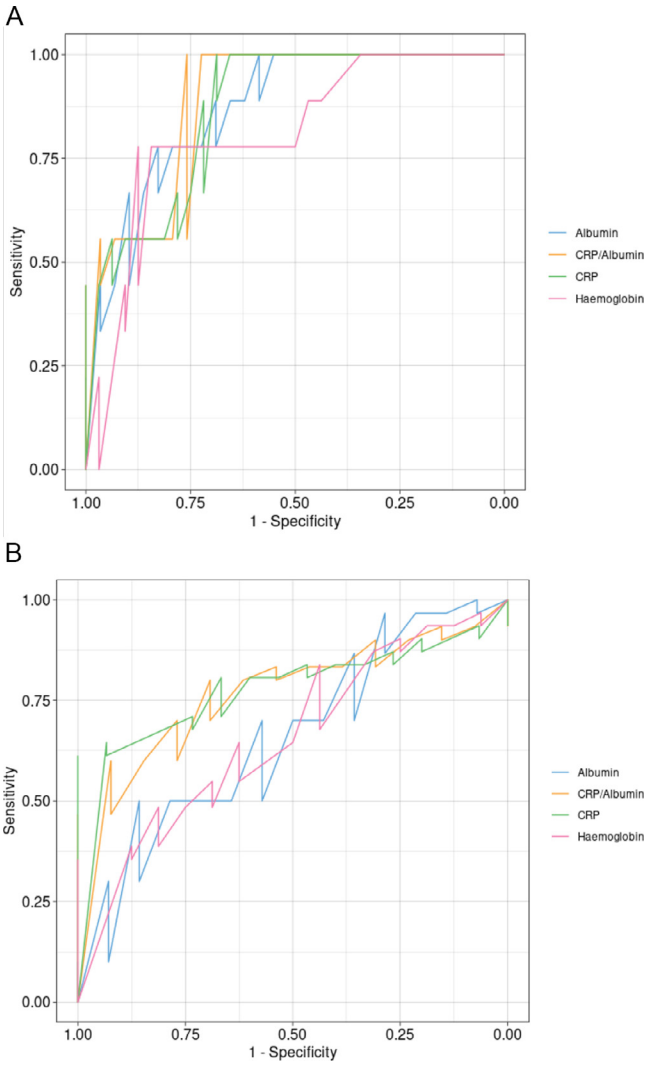

Fig. 3. A. ROC curves for CRP, albumin, CRP/albumin ratio and hemoglobin to predict the presence of deep ulcers in the prospective cohort. B. ROC curves for CRP, albumin, CRP/albumin ratio and hemoglobin to predict the presence of deep ulcers in the retrospective cohort.

Table 4
Area under the curve for receiver operating characteristic curves of CRP, albumin, CRP/albumin ratio and hemoglobin for the presence of deep ulcers in the two cohorts.

	Prospective cohort (n = 41)	Retrospective cohort (n = 46)
CRP	0.87	0.79
Albumin	0.87	0.66
crp/albumin ratio	0.89	0.77
hemoglobin	0.81	0.68

CRP: C-reactive protein.

The association between clinical severity and CRP elevation in UC has long been known [4]. Presence of systemic inflammation, measured initially by ESR and next by CRP level, is part of the modified Truelove and Witts criteria used to define acute severe UC [2]. To our knowledge, our study is one of the first to investigate thoroughly the link between CRP elevation and endoscopic severity in UC. We found that CRP elevation is a good surrogate marker for presence of deep ulcers. Most patients with CRP > 100 mg/L present with deep ulcers in the colorectal mucosa. Potential explanatory factors involve an increase production of inflammatory cytokines by monocytes in the context of a greater damage to mucosal barrier in patients with deep ulcers related to increased systemic transfer of luminal content such as bacterial peptides [15]. Noteworthy, none of the patients with disease extent restricted to the rectum displayed a CRP higher than 30 mg/l.

In acute severe UC, early identification of steroids non-responders is needed to avoid exposure to multiple immunosuppressants and delayed surgery [14]. The relevance of several biomarkers, such as CRP or albumin and endoscopic findings or fecal calprotectin have been investigated in that context. Buckell et al. in 1980 showed in a retrospective cohort of 40 patients with active severe UC that colonic dilatation and perforation were mostly seen in patients with deep ulcers [16]. Retrospective studies from the pre-biologics era showed that patients with active severe UC and deep ulcers were less prone to respond to steroids compared to patients without such lesions [5–7]. Recent studies found that CRP, albumin, fecal calprotectin and endoscopy at admission were robust predictors of non-response to steroids in acute severe UC [10,11,17]. However, in those studies, the total UCEIS and the Mayo score were used without discriminating between patients with severe or non-severe endoscopic lesions.

Here, we demonstrate that elevated CRP and decrease albumin are strong predictors for the presence of deep ulcers in acute UC both in a prospective and in a retrospective cohort. This is the plausible missing link between deep ulcers and steroid non-response. Evidence from clinical trials shows that ability of steroids to induce endoscopic healing of UC lesions is limited [18,19]. Our data suggest that patients with high CRP display deeper ulcers which steroids may not be able to act upon.

Available predictive indices in acute severe UC focus on response to steroids [11,17]. Few data exist on predictive factors of response to cyclosporine. In a retrospective study of 135 patients with steroid refractory-acute severe UC treated with cyclosporine, Cacheux et al. found that CRP > 45 mg/l and presence of deep ulcers at admission were associated with colectomy [20]. The picture is thought to be different with biological therapies because infliximab has been shown to be a potent mucosal healing agent in UC [18]. In pivotal randomized trials testing infliximab in acute severe UC, elevated CRP and presence of deep ulcers at therapy initiation were not predictive of response to therapy [21,22]. Similarly to what is observed with steroids, post-hoc analysis of the CYSIF trial comparing infliximab to cyclosporine in steroid refractory-acute severe UC found that cyclosporine was less prone to heal endoscopic lesions [23]. Consistent with our findings, pretreatment levels of CRP and albumin were not predictive of response to infliximab in a retrospective analysis of 54 patients treated for acute severe UC [13].

We acknowledge several limitations of our study. The relatively limited sample size hampered our ability to investigate the predictive value of biomarkers and endoscopic features for response to therapy. Thus, we restricted ourselves to descriptive objectives in a cross-sectional view of systemic inflammation and endoscopic severity which is currently not well depicted in the literature. In the retrospective cohort, endoscopic reports were retrospectively revised looking for deep ulcers. All included patients underwent colectomy, suggesting a selection bias of the most severe cases and a limited sample size. However, this ensured homogeneity of the study population and high reliability of lesions assessment in the whole colon on the retrospective specimen. Colonoscopy is not recommended during acute severe UC flare [24]. Staged colectomy was performed as recommended by ECCO guidelines[14] making histologic assessment of rectal and distal sigmoid ulcers impossible for the majority of patients. That is the reason why we combined the retrospective specimen evaluation to sigmoidoscopy findings. Conversely, we cannot exclude that patients in the prospective cohort without deep ulcers at flexible sigmoidoscopy and high CRP displayed deep ulcers in the transverse or right colon. Fecal calprotectin was not routinely available for all patients included in this study. In the retrospective cohort, CRP measurement right before colectomy was used to ensure homogeneity but could have been decreased by medical treatment received.

In conclusion, using both prospective and retrospective data, we showed that systemic inflammation measured by CRP elevation and hypoalbuminemia is strongly associated with deep ulcers in patients with active UC, especially in case of an acute severe episode. These biochemical and endoscopic severity features may be predictive of non-response to steroids and cyclosporine in the context of acute severe UC. Prospective trials must evaluate whether patients with acute severe UC and CRP > 100 mg/L at admission and/or deep ulcers should be treated with a biological as a first-line therapy.

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None.

Authors' contributions

Study concept and design; analysis and interpretation of data; statistical analysis; drafting of the manuscript; critical revision of the manuscript for important intellectual content; technical, or material support; study supervision: PR, DL.

Study concept and design; acquisition of data: ALC, AR, MM, AB, BL.

Acquisition of data and critical revision of the manuscript: ES, BC, BF, MU, TB, XT, FZ, FP.

All authors approved the final version of the manuscript.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethical concerns

This study was conducted in respect of the requirements set out in the applicable standard operation procedures of the Bordeaux University Hospitals Research Ethics Board.

Conflict of interest

PR declares consultancy fees from Abbvie, Amgen and Janssen.

FP declares consultancy fees, bords or transports from Abbvie, MSD, Takeda, Ferring, Janssen, Pfizer

FZ is a speaker for Janssen.

DL declares counseling, boards, transports or fees from Abbvie, Biogaran, Biogen, Ferring, HAC-pharma, Janssen, MSD, Novartis, Pfizer, Prometheus, Roche, Takeda, Theradiag, Tillots.

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