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Research Article

Is the C-Reactive Protein/Albumin Ratio a Reliable Marker for Predecting Steroid Response in Acute Severe Ulcerative Colitis?

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Abstract

Introduction: Identifying patients with acute severe ulcerative colitis (ASUC) who are refractory to corticosteroids early in the course of treatment is difficult, as no reliable predictive markers are available at admission. This study aims to evaluate whether the CRP/albumin ratio on days 1 and 3 of hospitalization can serve as an early predictor of response to intravenous steroids.

Materials and Methods: We retrospectively collected data from all admissions for ASUC in our center over 5 years. The optimal stool frequency, Lichtiger index, CRP, albumin, and CRP/albumin ratio (CAR) to predict steroid response at Day 1 and 3 was assessed by using the Receiver operating characteristic statistics.

Results: A total of 100 patients with acute severe ulcerative colitis (ASUC) were admitted. Among them, 79 patients responded to corticosteroids, while 10 patients required rescue therapy with infliximab (IFX), and 11 patients underwent colectomy. On day 3, stool frequency and Lichtiger index were significantly higher in the steroid-refractory group ($p < 0.001$). ROC analysis demonstrated that the day 3 CAR was a more accurate predictor of steroid responsiveness [AUC = 0.884, $p < 0.001$]. The optimal CAR threshold for predicting steroid response on day 3 was 2.13, with a sensitivity of 81% and a specificity of 83.5%.

Conclusions: Our study showed that a high level of CRP at Day 3 of hospitalization for ASUC and a low albumin level were early predictors of steroid responsiveness. We also showed that the combination of those two markers in a ratio improves their predictive ability.

Keywords: Acute Severe Ulcerative Colitis; Steroids; C-Reactive Protein; Albumin

Introduction

Acute severe ulcerative colitis (ASUC) is a medical emergency strictly defined by a frequency of bloody stools ≥6/day and at least one marker of systemic disturbance as defined by Truelove and Witts [1]. Intravenous corticosteroids were the first agents shown to be effective in ASUC, significantly improving patient outcomes [2]. Nevertheless, approximately 30% of patients exhibit an incomplete response and require either second-line rescue therapy or colectomy [3]. The management of ASUC has advanced with the introduction of infliximab (IFX), an anti-tumor necrosis factor agent. As a rescue therapy, IFX is now the preferred option by most gastroenterologists due to its efficacy, convenient administration, and potential use as a maintenance therapy [4].

Serum albumin plays a major role in IFX clearance in ASUC, therefore, an early initiation of IFX is mandatory before the onset of severe hypoalbuminemia which can compromise its efficacy [5]. The Oxford Index [6], was aimed to predict the need for colectomy at day three based on stool frequency and persistent CRP elevation and remained the most commonly used for so long. But, in the post-biologic era, this index had a sensitivity, specificity, and positive predictive value of 62%, 64%, and 56%, respectively, in predicting response to steroids [7]. These findings suggest that is no longer a useful tool to predict outcomes in ASUC. So as far, there is no simple algorithm to quickly predict corticosteroid responsiveness.

A simple tool based on biochemical markers could help identify high-risk patients who may benefit from the early initiation of accelerated IFX induction. We, therefore, sought to assess whether biological parameters such as CRP and albumin collected on admission and during hospitalization and combined in a ratio could identify patients with ASUC at high risk of non-response to IV steroids, intending to develop a tool that will help in selecting patients for early rescue therapy.

Materials and Methods

Study population

We conducted a retrospective review of all patients with ASUC admitted to the gastroenterology and hepatology department at the Ibn Rochd University Hospital in Morocco over 5 years from January 2020 to December 2024.

The outcomes of patients were extracted from our database. All patients have been diagnosed with ulcerative colitis (UC) using clinical, endoscopic, histological, and radiological criteria. The diagnostic of ASUC was carried out using the Truelove and Witts score. Any anterior medication exposure was recorded. All our patients received intravenous (IV) methylprednisolone at a dose of 0.8mg/kg from day one of hospitalization. Using the biochemical markers CRP and albumin that we extracted the CRP/Albumin ratio (CAR) was calculated. Stool frequency and Lichtiger score were recorded wherever available and analyzed in combination with biological markers. Clinical outcomes of patients were correlated to the CAR.

Outcome definitions

Steroid responsive

Patients were considered responders to corticosteroids if they progressed well on intravenous methylprednisolone with a switch to oral treatment and discharge from the hospital.

Steroid refractory

Patients not improving on intravenous steroids with the need to switch to biotherapy or emergency surgery.

Statistical analyses

Quantitative variables were reported as medians with interquartile ranges, and group comparisons were performed using the Mann–Whitney U test. Categorical variables were analyzed using the Chi-square test. Receiver operating characteristic (ROC) analysis was performed to determine the optimal CAR for steroid responsiveness on both days 1 and 3. Calculations were performed using JAMOVI Software (JAMOVI, 2.3.21). P values <0.05 were considered statistically significant. Data entry was done using Microsoft Excel 2019.

Results

We included in our study a total of 100 ASUC patients [male patients n= 55 (55%)]. An overall 51% presented as de novo UC. A total of 79 patients were steroid-responsive while the remaining patients (21%) had steroid-refractory ASUC and required rescue IFX or an emergency colectomy. We summarized in Figure 1 the outcomes of our patients. Table 1 reports the clinical characteristics and demographics of the patients, divided in two groups: steroid-responsive and steroid-refractory patients.

Data on stool frequency were available in all patients. The median day 3 stool frequency was higher in the non-responsive group (Median 10, IQR 2-14, $p < 0.001$). Day 3 Lichtiger index was also higher in the non-responsive group (Median 12, IGR 2-17, $p < 0,001$). Regarding endoscopic results, the median UCEIS was 7 in both groups.

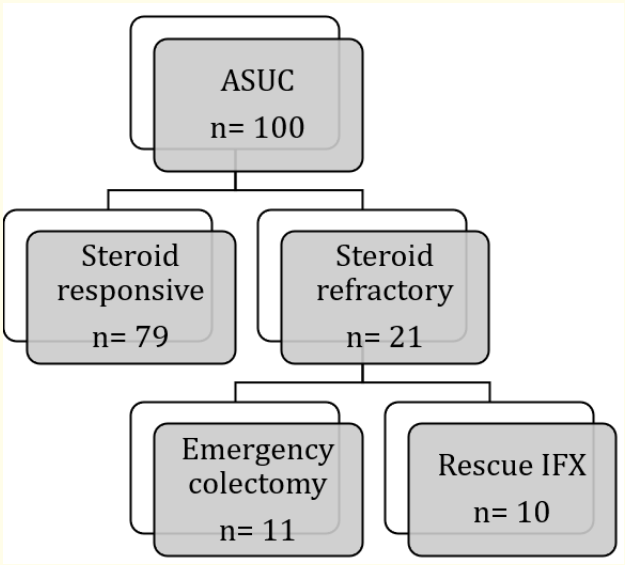

Figure 1: Outcomes of 100 patients admitted with ASUC. ASUC: acute severe ulcerative colitis; IFX: infliximab.

Complete data on CRP and albumin on day 1 and day 3 were available for all patients. Table 1 shows the median CRP and albumin on day 1 and 3 of the hospital stay. The median baseline CAR was 2.84 [IQR (0.20 to 9.68)], whereas the median day 3 CAR was 1.2 [IQR (0.06 to 8)].

First, we analyzed the relationship between biochemical data and steroid responsiveness, summarized in Table 2. Baseline CRP and Albumin were poor markers of steroid responsiveness. The ROC analysis showed that Day 3 CRP < 64 mg/L had a sensitivity of 76.2% and specificity of 83.45% ($p < 0.001$). Day 3 Albumin >31 g/L showed a sensitivity of 57% and specificity of 95.2% ($p < 0.001$). However, the strongest predictor for steroid responsiveness was the day 3 CAR, with an optimal cutoff of <2.13, sensitivity of 83.5%, specificity of 80.95%, and an AUC of 0.884 ($p < 0.001$), making it a highly reliable marker. The ROC curve for day 3 CAR in predicting steroid responsiveness is shown in Figure 2.

Table 1: Demographics and Biological Variables of 100 Patients Admitted With ASUC.

Patient characteristic	Steroid responsive n = 79	Steroid refractory n = 21	p-value
Gender Male	44	10	0.852''
Female	35	11	
Age at admission Median (IQR) (y)	29 (15-64)	26 (16-60)	0.081*
Disease duration Median (IQR)(m)	7.23 (0-108)	1.93 (0-25)	0.009*
Disease extent at diagnosis Pancolitis	41	18	0.052''
Left-sided colitis	33	3	
Proctitis	1	0	
Medication exposure before admission 5-ASA (oral or local)	30	2	0.010''
Immunosuppresses	14	2	
None	35	17	
Length of stay Median (IQR) (d)	10 (5-30)	25 (10-60)	<0.001*
The first presentation of UC (%)	44.3	76.2	0.026''
UCEIS Median (IQR)	7 (4-8)	7 (3-8)	0.243*
Day 1 stool frequency Median (IQR)	10 (3-20)	9 (4-16)	0.615*

Day 1 Lichtiger index Median (IQR)	12 (6-18)	12 (10-18)	0.757*
Baseline CRP Median (IQR) (mg/L)	85 (6-292)	76 (14-192)	0.941*
Baseline albumin Median (IQR) (g/L)	29 (16-45)	27 (18-26)	0.132*
Baseline CRP/albumin Median (IQR)	2.81 (0.2-9.7)	3.4 (0.54-9.6)	0.657*
Day 3 stool frequency Median (IQR)	5 (2-11)	10 (5-14)	<0.001*
Day 3 Lichtiger index Median (IQR)	8 (2-14)	12 (9-17)	<0.001*
Day 3 CRP median (IQR) (mg/L)	27 (2.3-165)	89 (24.6-176)	<0.001*
Day 3 albumin Median (IQR) (g/L)	32 (20-45)	25 (17-31)	<0.001*
Day 3 CRP/albumin Median (IQR)	0.97 (0.07-4.71)	3.96 (0.83-8)	<0.001*

*Mann-Whitney U test. ‘‘Chi 2 Test.

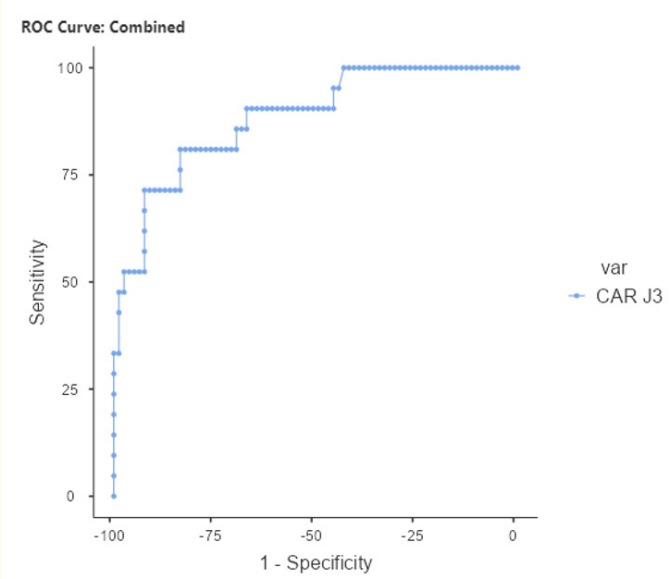

Figure 2: ROC curve for Day 3 CAR.

Discussion

The introduction of intravenous corticosteroids in the management of ASUC has significantly helped in reducing mortality by less than 1% while using IFX as a rescue therapy has contributed to low short-term colectomy rates [8].

Overall, 18% of our patients in this cohort were in the steroid-refractory group. This figure is close to that in the literature, as evidenced by a systematic review of 32 trials and cohort studies, which found an approximative response rate to steroids of 67%, while 27% required 2nd line therapy [9].

The optimal duration of IV corticosteroid therapy before deciding to rescue with IFX is unclear. Recent data from studies on ASUC suggest an early assessment of response to corticoids within 3 to 5 days of starting treatment to identify those at high risk of corticosteroid resistance [10], as a delay in resorting to 2nd-line treatment has consequences such as significant risk of postoperative complications and reduced efficacy of infliximab. In 2010, the Department of Gastroenterology at John Radcliffe Hospital conducted a study to determine the complications associated with delayed colectomy in ASUC [11]. Of the 80 patients included, 28% presented complications at D30 post-op. The impact of these complications was a longer duration of steroid treatment, with a median of 8 days.

A prospective cohort study was conducted in two centers in Amsterdam in 2016 [5]. Anti-TNF-naive adults with moderate-to-severe UC relapses were treated with infliximab. The results of the study approved that late administration of rescue therapy was associated with a significant risk of antibody formation but also of accelerated treatment clearance. This risk correlated inversely with albumin levels.

In line with the growing interest in combined inflammatory and nutritional biomarkers, Header., *et al*. evaluated the C-reactive protein/albumin ratio (CAR) as a marker for detecting severe acute ulcerative colitis in Egyptian patients [12]. This study showed that CAR values were significantly higher in patients with ASUC than in those with a moderate form of the disease, confirming the role of CAR as an integrated marker of disease severity reflecting both systemic inflammation and hypoalbuminaemia.

A more recent study that combined biological and endoscopic data to develop a score to predict response to IV corticosteroids on admission found that CRP and albumin levels were much more significant on days 3 and 5 than on admission, the p-value for both CRP and albumin was <0.0001 on days 3 and 5 [13]. In 2018 [14], the Colorectal Pathology Centre in Dublin conducted a retrospective study aimed at using, for the first time, the CRP/Albumin ratio in the early assessment of response to sorticosteroids during severe acute colitis. Of the 124 patients included in this study, 50% responded to steroids, while the other half required second-line treatment. Based on ROC statistics, the CRP/Alb ratio at D3 was a more accurate marker of steroid response than either day-3 CRP or day-3 albumin alone. The optimal CAR for predicting steroid response on day 3 in this study was 0.85, with sensitivity and specificity exceeding 70%. In our study, we also found that a reduction in the CRP/Albumin ratio at Day 3 correlated with steroid response. Patients with a CAR <2.13 were more likely to respond to steroids alone, whereas a persistently high CAR was associated with an increased risk of non responsiveness. This suggests that patients with a CAR ≥2.13 after 3 days of IV steroids may benefit from the immediate introduction of rescue infliximab to reduce the risk of colectomy.

Our study, representing the second worldwide exploration of using a ratio combining CRP and albumin to predict steroid response in severe acute ulcerative colitis, provides insights into the potential utility of this approach. However, despite this advancement, several limitations need consideration. Firstly, given the retrospective nature of our study, it may introduce bias and limit the ability to establish causality. Additionally, the sample size in our study was relatively small, potentially affecting the generalizability of our results to larger populations. However, future prospective studies with larger, more diverse cohorts are necessary to establish a universal threshold for the CRP/Albumin ratio in predicting steroid response.

Conclusion

In summary, our study demonstrated that day 3 CAR is a powerful marker for predicting the response to steroids in ASUC. It is an easy, inexpensive, and reliable predictor that can help in the early

introduction of rescue treatment in refractory patients. Early identification of high-risk refractory patients will allow us to initiate biotherapy and avoid colectomy, especially before albumin levels drop and the risk of complications increases further. But, this result needs to be validated in a large prospective cohort.

Acknowledgments

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