SYSTEMATIC REVIEWS AND META-ANALYSES

Systematic Review: Outcome Prediction in Acute Severe Ulcerative Colitis

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BACKGROUND AND AIMS: Approximately 1 in 4 patients with ulcerative colitis experiences a severe exacerbation of disease requiring hospitalization, termed acute severe ulcerative colitis (ASUC). These episodes pose a major burden on patients with ulcerative colitis and early prediction of their outcomes based on clinical data is crucial to optimize therapy. **METHODS:** A systematic review was performed using Embase and Medline for articles between 2000 and 2023. Studies obtained from the databases were uploaded on Covidence for screening by 2 independent reviewers. Quality appraisal for each study was done using the Critical Appraisals Skills Program depending on study design. **RESULTS:** A total of 48 eligible studies were included in the review. The key predictors of ASUC identified in this review included clinical, endoscopic, and radiographic biomarkers, which were summarized. The main outcomes assessed in the studies were intravenous corticosteroid failure, need for rescue therapy, and need for colectomy. Score-based predictions and some novel markers were also included in the results. **CONCLUSION:** Utilization of evidence-based predictors of outcome in ASUC could serve as a powerful tool in customizing therapeutic measures and a step forward toward personalized patient care. Despite promising candidates, there remains a significant opportunity to identify and test additional clinical and laboratory-based predictors, especially early in the hospitalization and as the clinical practice and medical therapies evolve.

Introduction

Ulcerative colitis (UC) is a chronic, inflammatory disease of the colon that classically presents as diarrhea, hematochezia, urgency, and abdominal pain.[1] Approximately, 1 in 4 patients with UC develops symptoms of significant severity to necessitate hospital admission. This complication is termed acute severe ulcerative colitis (ASUC). ASUC occurs within the first year of diagnosis in almost 34% of the cases.[2] Much like UC more broadly, the pathogenesis of ASUC is unknown, but likely involves dysfunctional immune responses, some unknown environmental triggers, and a genetic predisposition.[3]

Intravenous (IV) steroids remain the cornerstone of the therapy in ASUC. However, historically, almost 30% of patients fail to respond to IV steroids and require medical rescue therapy (eg, antitumor necrosis factor inhibitors, cyclosporine, and, more recently, JAK inhibitors) or ultimately surgical treatment.[4,5] ASUC is associated with significant morbidity, a length of stay ranging between 5 and 12.5 days,[6] progression to colectomy, and an estimated 1% mortality.[7,8] The rate of colectomy in UC has declined from approximately 7.8 per 100 person-years in 2007 to 4.2 per 100 person-years in 2016.[9] The use of new drugs, including JAK inhibitors, in the medical management of ASUC is promising. However, patient-specific prognostication remains challenging, and given the burden of this disease complication, the changing landscape of UC with the introduction of an increasing number of medications and increasing recognition of morbidity associated with medically refractory disease even after colectomy,[10] improving care for patients with ASUC remains paramount. To this end, we performed a systematic review of predictors of outcomes for patients with ASUC, including clinical biomarkers, endoscopic scores, and imaging. Our goal is that this systematic review can be used to refine a research agenda and summarize the evidence base for clinical prediction paradigms for the treatment of patients with ASUC.

Methods

Search Strategy and Quality Assessment

In this systematic review, Embase and MEDLINE were searched for full-text articles published between 2000 and March 1, 2023. Search strategies were developed in collaboration with a librarian. The terms used in the search included 'acute severe ulcerative colitis', 'severe acute ulcerative colitis', 'hospitalization', and 'inpatient'. Controlled vocabulary terms

were used when applicable. Results obtained from both searches were uploaded on Covidence on which 2 authors performed the title and abstract screening. Conflicts were resolved by a third independent author. Additional potentially related articles were retrieved from bibliographies of the included articles. Some studies that investigated score-based predictions were included even if they were published before 2000 because they are still clinically relevant in the current practice. After completion of a full-text screening for topic relevance, quality assessment was done using the Critical Appraisal Skills Program checklists based on the type of the study. Agreement for inclusion of the study depended on the quality and whether the studies explore novel biomarkers or predictors that were not previously investigated.

Inclusion and Exclusion Criteria

Studies were included based on the following requirements: (1) randomized controlled trials, (2) retrospective or prospective observational studies, or (3) case series investigating hospitalized patients with ASUC of all age groups. ASUC had to be diagnosed clearly based on standard endoscopic and clinical criteria. Studies using clinical prediction models for relevant ASUC outcomes or investigating any aspect related to ASUC disease course whether from a therapeutic, diagnostic, or prognostic aspect were included. Studies included examined predictors of clinically relevant outcomes, including steroid responsiveness, need for medical rescue therapy, need for in-hospital colectomy, and need for colectomy after hospitalization on varying time scales ranging from 30 days to 1 year. Exclusion criteria included abstracts, case reports, and articles not available as full text in the English language.

Results

One thousand two hundred ninety seven articles were obtained in the initial search of both databases and uploaded on Covidence, which identified 186 duplicates. Title and abstract screening was performed for 1085 articles. The flow diagram in Figure 1 depicts the review process. Seventy eight articles were eligible for full-text screening and 48 articles were included in the systematic review after quality assessment. The articles were grouped based on subtopics and summarized in separate sections accordingly. Figure 2 summarizes data from several studies that addressed predictors of colectomy in a forest plot generated on R. Tables 1 and 2 demonstrate the different predictors discussed in the study on day 1 and on or after day 3, respectively. The main sections were divided into clinical biomarkers, predictors in the pediatric population, comorbid infections affecting outcomes, endoscopic and radiographic factors, and score-based predictions of outcomes in ASUC.

Clinical Biomarkers for Prediction of Outcomes in ASUC

CRP/ albumin ratio. Both C-reactive protein (CRP) and albumin are known biomarkers for assessing inflammatory bowel disease (IBD). CRP is produced by hepatocytes and released into the bloodstream in response to inflammation.[41,42] Albumin is also made in the liver, but its synthesis is suppressed in inflammatory conditions.[41] Many studies have shown that the CRP/albumin ratio (CAR) has prognostic value in pancreatitis, cancer, and sepsis.[42,43] Specifically, a high CAR is associated with mortality and poor prognosis.[44]

Recent studies demonstrate that CAR can be used to determine disease severity in ASUC on day 1. In a retrospective study of 200 UC patients, 20% had mild disease, while 41% had moderate disease, and 39% had severe disease. CRP (mg/dL, $P = .0001$), albumin (g/dL, $P = .0002$), CAR ($P = .0001$), and erythrocyte sedimentation rate (ESR mm/h, $P = .0001$) were statistically significantly different among the 3 activity groups. CAR, CRP, and ESR values were statistically significantly higher in ASUC patients compared to nonsevere UC patients, while albumin values were significantly lower ($P = .001$). A cutoff value of 0.6 for CAR was a strong predictor in differentiating ASUC patients, with a sensitivity of 98%, specificity of 100%, and a positive predictive value (PPV) of 100%.[11] A second retrospective study included 149 patients, 79% with clinically active disease and 21% in remission. CRP, albumin, CAR, and ESR were similarly statistically significant in separating patients into groups according to disease severity ($P = .001$). The optimal cutoff value for predicting ASUC was also reported to be 0.6, with a sensitivity of 88.9%, specificity of 90.3%, and a PPV of 85.1%.[12]

CAR can also strongly predict steroid-refractory disease. In a retrospective study of 124 ASUC patients, CAR at day 3 was more accurate compared to CRP or albumin alone in predicting steroid responsiveness on the third day of inpatient treatment for ASUC (Area Under the Curve = 0.75, $P < .001$). With a cutoff of 0.85, day 3 CAR had a sensitivity of 70% and a specificity of 76%. CAR is an even stronger predictor when combined with measurements of stool frequency > 3 on the third day of treatment increasing its sensitivity to 72% and specificity to 83% (Relative Risk = 3.9, 95% Confidence interval [CI], 2.1–7.2).[27]

CAR, therefore, shows promise as a biomarker for ASUC disease severity and a predictor for steroid responsiveness.

Fecal calprotectin. Calprotectin is a cytosolic protein found predominately in neutrophils. Elevated fecal calprotectin (FCP) is a biomarker of IBD disease activity, as it reflects increased neutrophil migration into the intestinal lumen resulting from inflammation.[45]

FCP levels can be used to discriminate between patients with mild, moderate, and severe UC. A prospective observational cross-sectional study included 97 patients, 49 with ASUC and 48 with active UC. FCP levels were significantly higher in patients with ASUC than those with mild to moderately active UC (median 1776 μg/g vs 282 μg/g, $P < .001$) or moderately active UC (median 1776 μg/g vs 332 μg/g, $P < .001$). A FCP > 782 μg/g can be used to differentiate ASUC patients from patients with less severe disease with a sensitivity of 84%, specificity of 88%, and PPV of 87%.[13]
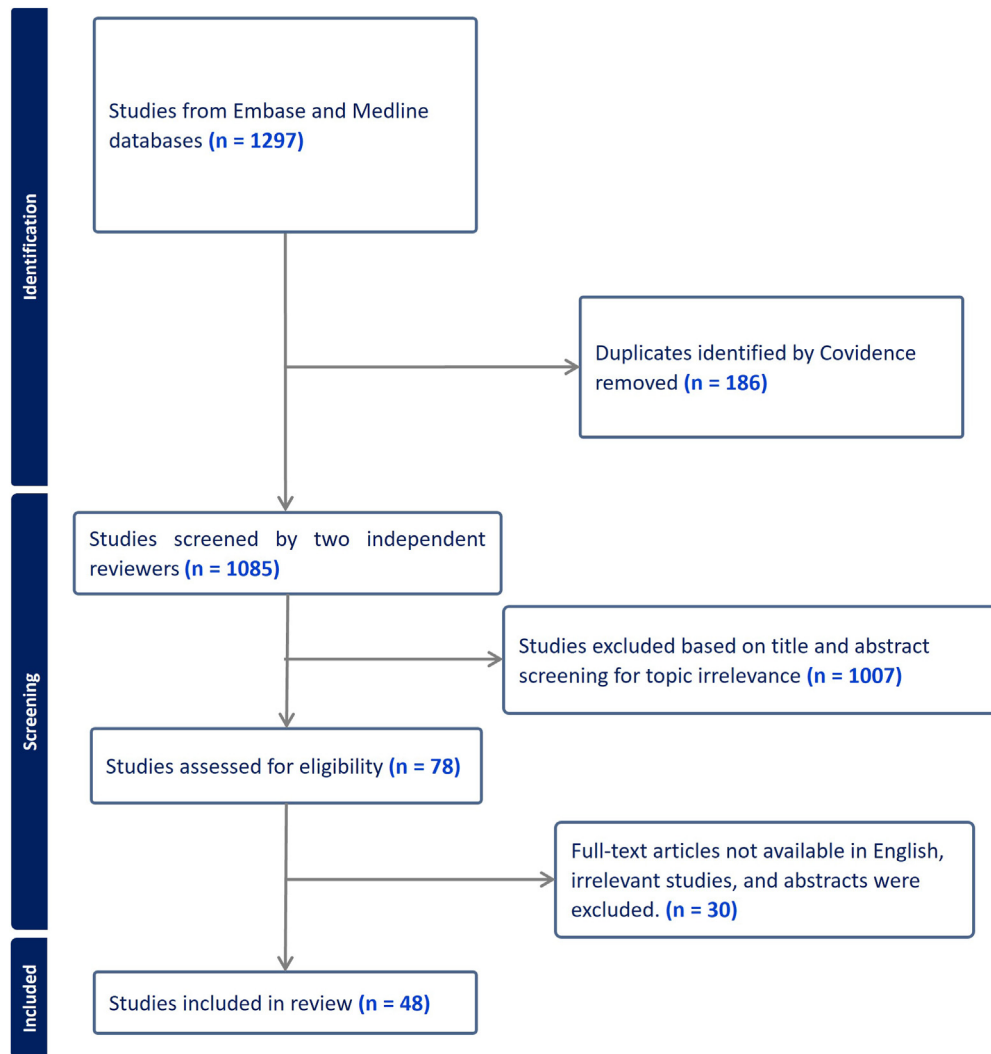
Figure 1. Flow diagram of systematic review.

FCP can also be used to predict steroid responsiveness in ASUC. In a prospective study of 117 ASUC patients, FCP most strongly correlated with UC endoscopic index of severity (r = 0.701, $P < .001$) compared to CRP, hemoglobin, platelet, and albumin levels in predicting outcomes of corticosteroid treatment.[14]

Finally, recent studies demonstrate that FCP predicts the need for medical or surgical rescue therapy in ASUC. In a multicenter retrospective cohort study of 147 patients (33% required medical rescue therapy, while 13% underwent emergency colectomy), FCP levels were significantly higher in patients requiring either therapy (median 1588 μg/g vs 1000 μg/g, $P = .02$) than those who did not. A FCP level > 800 μg/g was a strong independent predictor of the need for inpatient medical rescue therapy (Odds Ratio [OR], 2.61; 95% CI, 1.12–6.12). FCP levels were also significantly higher in patients requiring colectomy within 3 months of index hospitalization (median 1951 μg/g vs 1021 μg/g, $P = .018$). A FCP level > 800 μg/g was a strong independent predictor of the need for colectomy within 3 months of index hospitalization (OR, 2.88; 95% CI, 1.01–8.17) but did not significantly predict the need within 12 months of index

hospitalization.[15] In a second study of 90 ASUC patients (34% required colectomy), 86% of patients had levels higher than 500 μg/g (median 1020 μg/g). FCP levels were significantly higher in patients requiring emergency colectomy (median 1200 μg/g vs 887 μg/g, $P = .04$) than those who did not.[16]

Overall, FCP can distinguish ASUC patients from patients with less severe disease and strongly predict steroid responsiveness and the need for medical or surgical rescue therapy. However, in many hospitals, the clinical utility of FCP is limited by turnaround times of 1–2 weeks.[46]

Serum procalcitonin. Procalcitonin (PCT) is the peptide precursor of the hormone calcitonin, which plays a role in calcium homeostasis. PCT has been identified as a useful biomarker of gram-negative bacterial infection.[47] Its presence in circulation indicates inflammation, with elevated levels correlating with increased severity of infection.[48]

Recent studies have reported conflicting results on the role of serum PCT in ASUC. An observational study of 152 ASUC patients demonstrated that serum PCT ≥ 0.10 μg/L is a strong predictor of IV corticosteroid failure, second-line
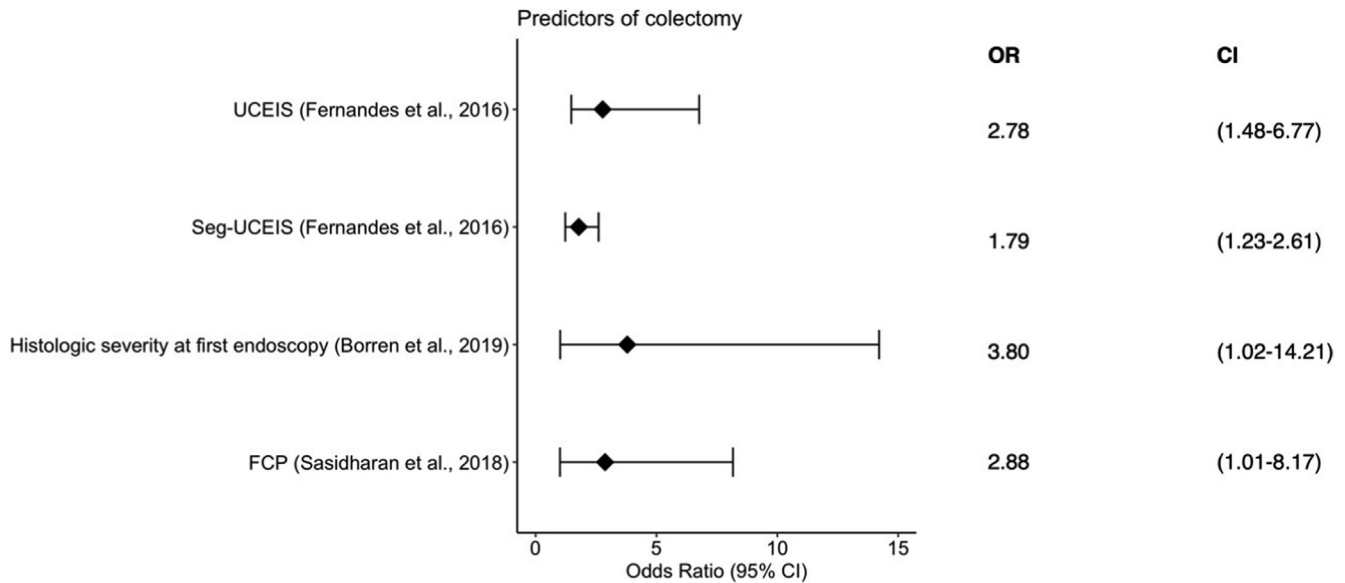
Figure 2. Forest plot of predictors of colectomy.

medical therapy failure, and short-term colectomy. Serum PCT is an even stronger predictor when combined with FCP levels.[28] However, a randomized controlled trial of 50 ASUC patients reported no association between PCT levels on admission or the third day of inpatient treatment and the need for second-line rescue therapy for corticosteroid failure.[49]

Sarcopenia. Sarcopenia is defined as a progressive reduction in skeletal muscle mass and strength.[50] While generally associated with age, sarcopenia is more common in IBD patients.[51]

Recent studies have supported the use of sarcopenia, as assessed by abdominal computed tomography (CT), in predicting medical and surgical rescue therapy in ASUC. Skeletal muscle mass can be assessed by CT at the level of the L3 vertebra by calculating a skeletal muscle index which involves the cross-sectional area and the height of an individual.[52] Sarcopenia is defined as a skeletal muscle index below the lowest quartiles specific for each sex.[53] A retrospective study of 254 ASUC patients found that 50% were sarcopenic. Compared with nonsarcopenic patients, sarcopenic patients received rescue therapy ($P < .001$) and underwent colectomy ($P = .001$) significantly more frequently during index hospitalization. Furthermore, sarcopenic patients were more likely to receive colectomy ($P = .001$) during the follow-up period.[17] Another study of 89 ASUC patients similarly reported that a larger proportion of sarcopenic patients were more likely to need either inpatient medical or surgical rescue therapy ($P = .02$). Sarcopenia was a strong predictor of medical or surgical rescue therapy even when controlling for age, gender, albumin, pancolitis, CRP, and body mass index (OR 3.98, CI 1.12–14.1). However, the study did not find an association between sarcopenia and colectomy rates 90 days or 1 year post-hospitalization.[18] Another retrospective study of 233 ASUC patients reported that sarcopenia was a strong predictor for IV corticosteroid failure ($P = .001$), need for colectomy after failure of medical rescue therapy ($P = .027$), and post-colectomy complications ($P = .012$).[19]

Sarcopenia is thus a novel, strong predictor for rescue therapy and postoperative outcomes in ASUC patients.

Predictors Studied Specifically in the Pediatric Population

Glucocorticoid bioactivity. To explore pediatric responsiveness to corticosteroid therapy, a study used a transactivation glucocorticoid bioassay to measure the biological activity of administered glucocorticoids in serum.[54] In the multicenter prospective study of 50 children with ASUC, 32% did not respond to corticosteroid therapy and required medical or surgical rescue therapy. However, they reported no association between glucocorticoid bioassay levels and short-term outcome of corticosteroids, as defined by Pediatric Ulcerative Colitis Activity index (PUCAI) score on the third and fifth treatment days and responsiveness to corticosteroids.[55]

Fecal osteoprotegerin. Osteoprotegerin (OPG) is a receptor protein produced by intestinal epithelial cells that binds the NF-KB ligand (RANKL).[56] In binding RANK-L, OPG inhibits osteoclast activation, thereby preventing bone tissue resorption.[57] OPG also plays a role in inflammation and immune cell apoptosis, which are relevant in IBD.[58]

In a study of 83 children with ASUC, 26.5% failed corticosteroid therapy and required infliximab rescue therapy. Median fecal OPG levels on the third day of treatment were significantly higher in nonresponders than those who did respond ($P = .007$). A fecal OPG > 50 pmol/L on the

Table 1. Numerical Day 1 Predictors of ASUC

Day 1 predictors	Outcome(s)
CRP (mg/dL)/ albumin (g/dL) > 0.6	Disease severity (Header et al., 2022[11]: SN = 98%, SP = 100%, n = 200; Sayar et al., 2018[12]: SN = 88.9%, SP = 90.3%, n = 149)
FCP	Disease severity (FCP > 782 μg/g) (Kedia et al., 2018[13]: SN = 84%, SP = 88%, n = 97) Steroid refractoriness (Xie et al., 2017,[14] correlated with UCEIS with r = 0.701, P < .001, n = 117) In-hospital rescue therapy (FCP > 800 μg/g) (Sasidharan et al., 2018[15]: OR, 2.61; 95% CI, 1.12–6.12, n = 147) In-hospital colectomy within 3 mo (FCP > 800 μg/g) (Sasidharan et al., 2018[15]: OR, 2.88; 95% CI, 1.01–8.17, n = 147; Ho et al.,[16] 2009: P = .04, n = 90)
Sarcopenia (skeletal muscle index [SMI] < lowest quartile for sex) • SMI: Cross-sectional area and height	In-hospital rescue therapy (Ge et al., 2022[17]: P < .001, n = 254; Cushing et al., 2018[18]: P = .02, n = 89) In-hospital colectomy (Ge et al., 2022[17]: P = .001, n = 254; Cushing et al., 2018,[18] P = .02, n = 89) Steroid refractoriness (Ge et al., 2021[19]: P = .001, n = 89) Postoperative outcomes (Ge et al., 2021,[19] n = 89)
Serum CMV DNA > 250	Steroid refractoriness (Roblin et al., 2011,[20] n = 42)
Mucosal CMV DNA > 2000	Steroid refractoriness (Jain et al., 2021[21]: SN = 53%, SP = 89%, n = 76)
C. difficile infection	In-hospital colectomy (Le Baut et al., 2021[22]: HR 3.73; 95% CI, 1.11–12.55, n = 270)
UCEIS ≥ 7 • Vascular pattern (0–2) • Bleeding (0–3) • Erosions and ulcers (0–3)	In-hospital rescue therapy (Corte et al., 2015[23]: n = 89)
Presence of megacolon and mucosal islands on abdominal X-ray	In-hospital colectomy (Mokhele et al., 2017[24])
ACE index • Albumin ≤ 30 g/L • CRP > 50 mg/L • Mayo endoscopic score = 3	Steroid refractoriness (Grant et al., 2021,[25] P < .001)
ADMIT-ASC ≥ 3 • Admission CRP ≥ 100 mg/ L (1 point) • Albumin ≤ 25 g/L (1 point) • UCEIS score ≥ 4 (1 point) or UCEIS score ≥ 7 (2 points)	Steroid refractoriness (Adams et al., 2023[26])
Le Baut et al. score • C. diff infection • CRP > 30 mg/L • Albumin < 30 g/L	In-hospital colectomy (Le Baut et al., 2021[22])

ADMIT-ASC, Admission Model for Intensification of Therapy in Acute Severe Colitis; ASUC, Acute Severe Ulcerative Colitis; CI, confidence interval; CMV DNA, cytomegalovirus DNA; CRP, C-reactive protein; FCP, fecal calprotectin; HR, hazard ratio; OR, odds ratio; SN, Sensitivity; SP, Specificity; UCEIS, Ulcerative Colitis Endoscopic Index of Severity.

third treatment day can be used to predict responsiveness to corticosteroid therapy with a sensitivity of 71% and specificity of 69%.[29]

Histologic features. The Geboes histological scoring system has been previously used to assess inflammation in pediatric UC.[59] The system is a 6-grade classification scale that evaluates structural changes, inflammatory infiltrate, presence of neutrophils in the lamina propria, presence of neutrophils in the epithelium, crypt destruction, and ulceration.[60] A recent study evaluated the prognostic value of the Geboes system in predicting colectomy in 50 children with ASUC (32% of which required surgical rescue therapy).

There were no significant differences in histologic features of inflammation between patients who required colectomy within 90 days of hospitalization and those who did not.[61]

Serum inflammatory cytokines. Cytokines play critical roles in inflammation, specifically interleukin (IL)-6, IL-1 β, and tumor necrosis factor (TNF-α), which stimulate the release of additional proinflammatory cytokines.[62] A prospective multicenter study aimed to evaluate whether cytokine levels could be used to predict responsiveness to corticosteroids in pediatric ASUC patients. Serum samples were obtained during admission at multiple intervals and at discharge from 79 children hospitalized for inpatient

Table 2. Numerical Day 3+ Predictors of ASUC

Day 3+ predictors	Outcome(s)
CRP (mg/dL)/ albumin (g/dL) > 0.85	Steroid refractoriness (Gibson et al., 2018[27]: SN = 70%, SP = 76%, n = 124)
CRP (mg/dL)/ albumin (g/dL) > 0.85 + stool frequency > 3	Steroid refractoriness (Gibson et al., 2018[27]: SN = 72%, SP = 83%, n = 124)
Serum PCT ≥ 0.10 μg/L	In-hospital rescue therapy (Wu et al., 2019,[28] n = 152) In-hospital colectomy (Wu et al., 2019,[28] n = 152)
Fecal OPG > 50 pmol/L	Steroid refractoriness (pediatric) (Sylvester et al., 2011[29]: SN: 71%, SP: 69%, n = 83)
Segmental index scoring of the rectum and sigmoid (seg-Mayo and seg-UCEIS)	Steroid refractoriness (Fernandes et al., 2016[30])
Bowel ultrasound • Colonic wall thickness (CWT) • Loss of normal colonic wall stratification (CWS) • Colonic wall flow • Presence of hyperechoic lymph nodes	Steroid refractoriness (CWT > 3.4 mm, pediatric) (Scarallo et al., 2020,[31] SN: 92%, SP: 52%, n = 52) In-hospital rescue therapy (CWT > 6 mm) (Smith et al., 2021,[32] Ilvemark et al., 2022[33])
Oxford index Either: 1. > 8 bowel movements on day 3 2. 3–8 bowel movements on day 3 with CRP > 45 mg/L	Steroid refractoriness (Travis et al., 1996,[34] n = 49)
Swedish index > 8 • Stool frequency/day + 0.14 × CRP (mg/L)	Steroid refractoriness (Lindgren et al., 1998[35]: SN = 75%, SP = 75%)
Edinburgh score ≥ 4 • Mean stool frequency by day 3 (< 4: 0 points, 6–9: 2 points, > 9: 4 points) • Hypoalbuminemia on day 1 (≤ 30 g/L: 1 point) • Colonic dilation on abdominal X-ray on day 3 (> 5.5 cm: 4 points)	Steroid refractoriness (Ho et al., 2004[36]: SN: 85%, SP: 75%, n = 167)
Seo score ≥ 200 • 60 × blood in stool + 13 × bowel movements + 0.5 × ESR – 4 × hemoglobin (g/dL) – 15 × albumin + 200	In-hospital colectomy (Seo et al., 2002[37]: SN: 71%, SP: 94%)
AIIMS index • UCEIS ≥ 7 • FCP > 1000 μg/g on day 3	Steroid refractoriness (Sahu et al., 2022[38])
PUCAI • Abdominal pain • Rectal bleeding • Stool consistency • Stool frequency • Nocturnal schools • Activity level	In-hospital rescue therapy (PUCAI > 70 on day 5, pediatric) (Turner, Mac, et al., 2010[39]) In-hospital rescue therapy (PUCAI ≥ 65 on day 5, adult) (Atia et al., 2021,[40] n = 153) Steroid refractoriness (PUCAI ≥ 45 on day 5, adult) (Atia et al., 2021,[40] n = 153)

AIIMS index, All India Institute of Medical Sciences index; ASUC, Acute Severe Ulcerative Colitis; CRP, C-reactive protein; CWS, Colonic Wall Stratification; CWT, Colonic Wall Thickness; ESR, erythrocyte sedimentation rate; FCP, fecal calprotectin; OPG, Osteoprotegerin; PCT, procalcitonin; PUCAI, Pediatric Ulcerative Colitis Activity index; SN, Sensitivity; SP, Specificity; UCEIS, Ulcerative Colitis Endoscopic Index of Severity.

corticosteroid therapy. Of these children, 29% required rescue medical therapy. Enzyme-linked immunosorbent assay–based cytokine assays were used to measure serum cytokine levels. Only levels of serum IL-6 were statistically significantly different between patients who responded to corticosteroids and those who did not ($P = .003$).[63]

Interaction Between Infections and Outcomes in ASUC

Cytomegalovirus infection. Cytomegalovirus (CMV) is a herpesvirus prevalent in up to 40%–100% of the general population and remains latent in a human after initial infection.[64] CMV infection in patients presenting with moderate-to-severe UC flares (diagnosed on histopathology) has been associated with more severe disease, as indicated by higher Mayo scores on presentation.[65,66] Additionally, CMV infection in ASUC patients has been associated with increased risk of hospitalization,[66] increased steroid-resistance,[65,20,21] and increased need for rescue therapy.[65,21,67] Some studies have also demonstrated increased risk of colectomy in the short term,[21] although this has not borne out to be statistically significant in other studies.[65,66,68] Some of this discordance

may be due to diverse methods of CMV detection used in different studies—including serology, polymerase chain reaction analysis, and histological assessment by H&E and/or immuno-histochemistry—which can vary greatly in terms of sensitivity and specificity for diagnosis of CMV infection and disease.

In a prospective study of 42 consecutive patients hospitalized for moderate-to-severe UC, IgG antibodies to CMV were found in 59.5% of patients and CMV DNA was detected in the inflamed tissue of 38%. CMV DNA load was associated with steroid-refractory disease (risk ratio 4.7; 95% CI 1.2–22.5). A CMV DNA load > 250 copies/mg was strongly predictive of resistance to 3 drug treatments.[67]

In another study of 76 ASUC patients, 39% failed steroids. 16% required colectomy. CMV DNA load was significantly higher in the mucosa of steroid nonresponders compared to responders (3454 copies/mg vs 116 copies/mg, $P = .004$). A mucosal CMV DNA load > 2000 copies/mg could distinguish steroid nonresponders from responders with a sensitivity of 53% and a specificity of 89%. Furthermore, a mucosal CMV load > 2000 copies/mg could be used as a significant predictor for steroid failure and colectomy upon admission (OR 10.2, 95% CI 2.6–39.7).[21]

Mucosal CMV DNA may therefore predict steroid-refractory ASUC and resistance to treatments, although the significant interinstitutional heterogeneity in assays for CMV limits the broad application of these findings.

Clostridioides difficile infection. In patients with UC, *Clostridioides difficile (C. diff)* infection has been associated with increased risk of colectomy, postoperative complications, and increased mortality.[69] Studies focusing on C. *diff* infection in ASUC populations are limited, but likely show similar findings. A retrospective study of 270 ASUC patients demonstrated an association between *C. diff* infection and 1-year colectomy rates (HR 3.73; 95% CI, 1.11–12.55).[22] As *C. diff* infection in the general elderly population has been associated with increased rates of severe colitis,[70] it is possible that *C. diff* infection could potentially be related to worse outcomes of patients aged > 65 years presenting with ASUC. Overall, *C. diff* infection should be treated in ASUC population aggressively if found on presentation, with escalation of immunosuppressive therapy thought to be safe and recommended.[71,72]

Other infections. There are very limited data regarding outcomes for more common bacterial and non-CMV viral enteric infections. Generally, infection with these does not appear to confer worse clinical outcomes. A retrospective study of 147 ASUC patients tested for viral enteropathogens (polymerase chain reaction testing for adenovirus, rotavirus, or norovirus) showed no association with worse CRP, Mayo endoscopic scores, length of hospital admission, steroid responsiveness, requirement of rescue therapy, or colectomy rates compared to patients with ASUC alone.[73]

Endoscopic Scores and Outcomes

Endoscopy, coupled with other clinical data, can be used to assess disease severity, guide treatment, and predict outcomes and colectomy requirements in ASUC. Extent of lesions (eg, pancolitis, subtotal colitis, left colon) and lesion characteristics (eg, friability, vascular patterns, bleeding, and ulcerations) has been shown to correlate with disease severity.[74] In a retrospective review of severe UC patients (defined by more than 6 episodes of diarrhea with blood or mucous a day and other biomarkers such as elevated temperature and ESR), 92.7% had pancolitis.[75] At least 9 endoscopic-based scoring systems for UC rely on location and characteristics of lesions to measure severity.[74]

Severity of endoscopic findings in ASUC may correspond with escalation of treatment from corticosteroids to "rescue" therapies.[23] For instance, a retrospective study of 41 ASUC patients found that the median Ulcerative Colitis Endoscopic Index of Severity (UCEIS) was higher for patients requiring initiation infliximab or cyclosporine; they suggest that a UCEIS ≥ 7 serves as a potential predictor for rescue therapy needs. In another retrospective analysis of 108 ASUC patients, segmental index scoring of the rectum and sigmoid (seg-Mayo and seg-UCEIS) was significantly higher in patients who were steroid-refractory. However, there was no endoscopic score associated with the need for rescue therapy.[30]

Multiple studies have demonstrated higher rates of colectomy in patients with severe lesions and worse endoscopic scores.[74,30,76] A study of 49 ASUC patients who underwent 2 sigmoidoscopies during a single hospital admission reported that of the patients who showed improvement on the second endoscopic evaluation, none required surgical intervention. In contrast, almost half of the patients who demonstrated persistent or worsening disease required colectomy. Histologic severity during the first endoscopy was independently associated with a higher risk of colectomy.[76]

Imaging Studies and Outcomes

Radiologic imaging findings have been shown to correlate with known markers of ASUC. Three studies found that megacolon and mucosal islands on admission of abdominal X-ray independently predicted colectomy risk.[24] On the other hand, a retrospective study of 98 hospitalized ASUC patients found that biomarkers and abdominal X-rays were similar in patients with and without CT; moreover, CT findings were similar in patients who underwent colectomy and those who were managed medically.[77] Most recently, Hafeez et al. developed a magnetic resonance imaging total colonic inflammatory score based on components including haustral loss and colonic dilation, which correlated with CRP and stool frequency. This score also correlated with length of inpatient stay, while CRP and stool frequency did not.[78]

Imaging also plays a role in predicting responses to corticosteroids and need for salvage therapy. A study of 52 children with ASUC evaluated the value of bowel ultrasound performed within the third day of treatment in predicting corticosteroid failure. Of these children, 52.2% were

nonresponsive to corticosteroids and required second-line medical therapy. Loss of normal colonic wall stratification was more frequently observed in corticosteroid non-responders ($P < .001$). Nonresponders had significantly higher mean values of colonic wall thickness (CWT) (5.14 mm vs 3.69 mm, $P < .0001$) and had enhanced colonic wall vascularization ($P < .0001$). A CWT > 3.4 mm predicted responsiveness to corticosteroid therapy with a sensitivity of 92%, specificity of 52%, and a PPV of 67%.[31] Similarly, a pilot study of 10 ASUC patients who underwent a gastro-intestinal ultrasound within 24 hours of admission showed that a CWT > 6 mm was associated with the need for infliximab salvage therapy.[32] Reduction in CWT following initiation of IV corticosteroids has been used to identify corticosteroid responders and has the potential to guide timely initiation of rescue therapy.[33]

Score-Based Predictions of Outcomes

Multiple indices using clinical, radiologic, and/or biologic parameters have been created to predict patients most likely to fail first-line medical therapy during UC flares and can guide use of medical rescue therapy and/or need for colectomy. In adults, the Oxford (Travis), Edinburgh (Ho), Swedish (Lindgren), and Seo scores are the most used. However, these scores have limitations most notably that they are calculated on day 3 after admission (to assess steroid responsiveness) and many were created before the widespread use of biologic agents. Thus, scoring systems including the ACE Index[25] have been created to predict outcomes earlier and to account for more up-to-date treatment paradigms.

The Oxford index (1996) is based on a prospective study of 49 ASUC patients admitted to an Oxford hospital. Patients treated with IV steroids who on day 3 still had stool frequency of > 8 bowel movements (BM) daily or had 3–8 BM daily with CRP > 45 mg/L had a significantly higher risk of failing IV steroids, and 85% of patients in these categories required colectomy during the study follow-up period.[34]

The Swedish index (1998) uses CRP and stool frequency on day 3 of IV steroid treatment to predict steroid resistance. The score is calculated as stool frequency/day + $0.14 \times$ CRP (mg/L), with a score > 8 on the third day of admission predictive of a high risk of IV steroid failure and colectomy within 30 days with a sensitivity and specificity of 75%.[35] Notably, at the time of these studies, there were limited rescue therapies available and colectomy was often the next step in ASUC patients with steroid failure.

Subsequently, the Edinburgh score (2004) is based on mean stool frequency by day 3 of admission (< 4/d-0 points, 4–6/d −1 point, 6–9/day - 2 points, > 9/d - 4 points), hypoalbuminemia on admission ($\leq$ 30 g/L - 1 point), and colonic dilation on abdominal X-ray on day 3 of admission (> 5.5 cm - 4 points). In a retrospective study of 167 patients, high risk was defined as a total score $\geq$ 4, intermediate risk total score 2–3, and low risk total 0–1, with medical therapy failure rates 85%, 43%, and 11%,

respectively, and a score of $\geq$ 4 predicting nonresponse to IV steroids with a sensitivity of 85% and specificity of 75%.[36]

The Seo index is calculated as $60 \times$ bloody stools $+ 13 \times$ BM $+ 0.5 \times$ ESR $- 4 \times$ hemoglobin $- 15 \times$ albumin $+ 200$; however, its utility is limited as it was studied after 1 and 2 weeks of medical therapy. A score of $\geq$ 200 after 2 weeks of therapy strongly predicts colectomy with a sensitivity 71% and specificity 94%.[37] Furthermore, the All India Institute of Medical Sciences index, which uses UC Endoscopic Index of Severity $\geq$ 7 and day 3 fecal calprotectin > 1000 ug/g, has also been proposed. A recent prospective study of 47 patients suggested that the All India Institute of Medical Sciences index predicts steroid failure with similar or better specificity and PPV than the Oxford criteria, although further studies are needed and widespread application remains limited by calprotectin turnaround times.[38]

As we introduced, an important limitation of these indices is they are calculated on day 3 of ASUC hospitalization. There has been an increasing need to predict IV steroid responses as early as possible, ideally on day of presentation. This would allow clinicians to accelerate the introduction of medical rescue therapies beyond steroids and to facilitate earlier surgical consultation and assessment for potential colectomy. Therefore, indices have been proposed using data within the first 24 hours of admission to predict the likelihood of steroid failure. Using the ACE (Albumin, CRP, and Endoscopy) Index, patients who have CRP > 50 mg/L, albumin $\leq$ 30 g/L, and Mayo endoscopic score of 3 on presentation were found to have a significantly elevated risk of steroid nonresponsiveness (Area Under the Curve 0.754, $P < .001$ with PPV 78.1 and negative predictive value [NPV] 87.1).[25] Early studies using this index in ASUC patients have shown that it can differentiate steroid responders from nonresponders (PPV = 50%, NPV = 86.3%).[79]

Similarly, the Admission Model for Intensification of Therapy in Acute Severe Colitis uses admission CRP $\geq$ 100 mg/L (1 point), albumin $\leq$ 25 g/L (1 point), and UCEIS score of $\geq$ 4 (1′ point) or $\geq$ 7 (2 points), for which a score of $\geq$ 3. It was found to be predictive of steroid non-responsiveness in the original Oxford cohort and 84% predictive using validation cohorts from Australia and India.[26] Other studies have recommended using indices without imaging or endoscopic studies, which requires additional time/resources. For example, a study of 270 ASUC patients found that having at least 3 of the following criteria: previous treatment with TNF antagonists or thiopurines (HR 3.86), *C. diff* infection (HR 3.73), CRP > 30 mg/L (HR 3.06), and serum albumin < 30 g/L (HR 2.67) was associated with increased risk of colectomy within 1 year.[22] These proposed indices are still new and require further validation in both prospective and larger cohorts of ASUC patients but begin to move the window of critical assessment of risk and disease severity to earlier in the hospitalization.

In pediatric practice, the PUCAI score, comprised of 6 clinical symptoms/signs (abdominal pain, rectal bleeding,

stool consistency, stool frequency, nocturnal stools, and activity level), is used on day 3 and day 5 of hospitalization to assess IV steroid responsiveness. This score has been shown to be superior to the Oxford, Swedish, and Seo indices, as well as CRP and FCP, and is used regularly in pediatric patients in 2-step decision-making. A score > 45 on day 3 (PPV = 43%, NPV = 94%, $P < .001$) or a score > 70 on day 5 (PPV 100%, NPV = 79%, $P < .001$) predicts steroid failure.[39] A retrospective study of 153 adult patients with ASUC showed that PUCAI $\geq$ 45 on day 3 (PPV 54%, NPV = 83%) and PUCAI $\geq$ 65 on day 5 strongly predicted the need to initiate second-line therapy.[40] In this study, PUCAI on day 3 was similar to the Oxford and Swedish scores, but superior on day 5 in predicting colectomy,[80] indicating that it may also have some clinical efficacy in adults, although this requires further studies.

Conclusion

This systematic review outlines the current evidence for clinical, endoscopic, and radiographic biomarkers and multiparameter clinical scores that predict clinically meaningful outcomes in ASUC. As we consider using these data to improve care for patients with ASUC, we must consider them in the context of the medical care that was available at the time the biomarker or score was developed. If steroid responsiveness is still an appropriate delineator remains a critical question, that is, should medical rescue therapy beyond steroids be considered for all patients requiring hospitalization? What is the optimal time to determine steroid responsiveness? What is the optimal time to initiate medical rescue therapy? These are questions that require study with the backbone of biomarkers reviewed here, but there remains a critical need for a more dynamic assessment of biomarkers and important clinical outcomes especially as the treatment landscape continues to evolve.

The data here are meant to inform evidence-based practice. Even with the limitations as they are, there remains an opportunity to capitalize on this evidence and prioritize integration of some of these biomarkers into clinical decision-making tools that assist clinicians in making safer and data-informed decisions. We should be pushing to imagine an evidence-based hospitalization for patients with ASUC that can evolve. We need both retrospective and prospective cohorts across institutions to gain necessary sample size for prompt identification and testing of biomarker candidates/clinical scores as they emerge. It is only with this coordinated effort that accelerated improvement can occur for this important clinical complication of UC.

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