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ORIGINAL ARTICLE

Delayed Initiation of Rescue Therapy Associated with Increased Length of Stay in Acute Severe Ulcerative Colitis

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Abstract

Background Reducing hospitalization length of stay (LOS) for acute severe ulcerative colitis (ASUC) will reduce healthcare costs, mitigate hospitalization-associated risks (e.g., venous thromboembolism), and improve quality of life.

Methods A chart review was performed of all adult ASUC-related hospitalizations at University of California, San Francisco, from July 1, 2014, to December 31, 2017. Univariate and multivariate analyses were performed to identify factors associated with LOS < 7 days versus ≥ 7 days. A subgroup analysis was performed excluding patients who underwent colectomy during hospitalization.

Results A total of 95 ASUC-related hospitalizations were identified. The initial univariable analysis identified the following factors associated with LOS ≥ 7 days ($P < 0.05$): higher maximum heart rate in the first 24 h, higher C-reactive protein, being biologic therapy naïve, and a later hospital day of biologic therapy initiation. On mixed model multivariable analysis, later hospital day of biologic initiation was associated with increased LOS ≥ 7 days (OR 3.1 95% CI 1.2–7.56, $p = 0.012$).

Conclusions We identified multiple predictors for longer hospital LOS, including factors related to disease severity (non-modifiable) and treatment (potentially modifiable). Importantly, this study identified biologic naïve treatment status and delayed inpatient biologic therapy initiation as predictors of longer LOS (≥ 7 days) in patients who did not ultimately require colectomy during their hospital stay. Potentially modifiable strategies to reduce LOS may include early communication and patient education about biologic therapy in both the inpatient and outpatient setting.

Keywords IBD · Ulcerative colitis · Length of stay · Hospitalization · Biologic therapy

Introduction

Inflammatory bowel disease (IBD), which encompasses Crohn's disease and ulcerative colitis, impacts more than 3.1 million individuals in the USA [1]. Acute severe ulcerative colitis (ASUC) is a medical emergency characterized by severe disease according to Truelove and Witts criteria: more than 6 bloody stools per day plus tachycardia > 90 beats per minute (bpm), fever > 37.8 °C, hemoglobin < 10.5 gm/dL, and/or erythrocyte sedimentation rate (ESR) > 30 mm/h [2]. A severe IBD flare often requires hospitalization, which incurs significant economic costs. Mean annual costs for ulcerative colitis have been estimated to be $10,833, with hospital care accounting for over one-third of the cost of ulcerative colitis management [3]. Additionally, prolonged hospitalization puts patients at risk for hospital acquired complications such as venous thromboembolism, opiate analgesic exposure, and *Clostridioides difficile* infection [4, 5].

Hospital length of stay (LOS) is often used to gauge the efficiency of a healthcare facility, with the national average hospital LOS being 4.5 days [6]. IBD hospitalizations are longer (mean LOS 5.6 days) [7, 8],with some studies reporting mean LOS as high as 16.2 days for patients hospitalized with IBD flares [8–10]. At our institution, the median LOS for acute severe ulcerative colitis (ASUC) is 7.4 days [11]. The association between direct cost and hospital LOS is well established for IBD [12]. Reducing LOS for patients with IBD has the effect of both improving quality of life

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and reducing healthcare costs associated with the disease [13, 14].

The aim of this study was to identify factors that are predictive of prolonged hospital LOS in patients with ASUC and to determine modifiable factors that may minimize LOS or allow for early mobilization of resources to prevent complications of prolonged stay.

Methods

Participants

All ulcerative colitis-related hospitalizations at University of California, San Francisco, from July 1, 2014, to December 31, 2017, were reviewed as part of a quality improvement project spanning that time frame [11]. The inclusion criteria were patient age ≥ 18, ulcerative colitis as the primary reason for hospitalization, and receipt of intravenous corticosteroids. Subjects hospitalized from July 1, 2014–June 30, 2016, were identified retrospectively using hospitalization ICD-9 and ICD-10 codes associated with ulcerative colitis. From July 1, 2016–December 31, 2017 (the set end point of the quality improvement project), subjects were identified prospectively using hospitalization diagnostic codes as well as the daily gastroenterology consult service census.

Procedures

All data were collected from the electronic health record. Data collected included age, gender, disease duration, historical extent of disease, current tobacco use, previous number of ulcerative colitis-related hospitalizations, medication treatment history, and medications at the time of admission. Details of the hospitalization and care rendered were also collected, including vital signs and diagnostic test results, medications administered, consultations provided, and discharge medication prescriptions. Hospital readmission and colectomy within 90 days of discharge were also assessed. Patients who received colectomy during the hospitalization were included in the primary analysis. LOS in patients who receive colectomy during the hospitalization may be affected by unique factors, including postoperative complications. As such, a subgroup analysis was performed excluding patients who underwent colectomy during hospitalization to determine risk factors for prolonged LOS without potential confounding from postsurgical factors.

LOS was defined as beginning at the time of first vital signs until the last set of vital signs were collected on the day of discharge. Given that the median LOS for hospitalized ulcerative colitis patients at the study institution is 7 days, we sought to compare those with LOS greater than or equal to 7 days to those with LOS less than 7 days. During the study period, a quality improvement initiative was implemented to standardize gastroenterology consultant recommendations and improves delivery of evidence-based care [11]. LOS reduction was not the primary aim of this QI initiative. Study procedures were compliant with the Health Insurance Portability and Accountability Act. The Institutional Review Board of the University of California, San Francisco, approved the study.

Statistical Analyses

Our primary outcome was to identify independent predictors of LOS in ulcerative colitis patients admitted with acute flare requiring intravenous corticosteroids. Continuous parameters were reported as median and interquartile range, and discrete parameters were reported as number and percent (%). Comparisons were made with Mann–Whitney U tests for continuous data and Pearson Chi-square tests for categorical data. Univariable analysis was performed to identify factors associated with hospital LOS < 7 days versus ≥ 7 days. A multivariable model included clinically significant variables chosen a priori from candidate variables with $p \leq 0.1$ in univariable analysis. With these chosen covariables, logistic regression analysis was then performed to assess the association between LOS and clinical characteristics prior to and during hospitalization. A p-value < 0.05 was considered statistically significant for all analyses. Data were analyzed using STATA v16.1 (College Station, Texas).

Results

Patient Characteristics

Ninety-five ASUC-related hospitalizations met the criteria for study inclusion. Median patient age was 35 years, and 68% were female. The median ulcerative colitis disease duration was 4.8 years. The median LOS was 6.8 days (IQR 4.6–10.7). Fifty patients had a LOS < 7 days, and 45 patients had a LOS ≥ 7 days. For the 15 patients who underwent colectomy during the hospital stay, median time to colectomy was 6.6 days.

For patients who had a LOS < 7 days as compared with those with LOS ≥ 7 days, there was no significant difference in gender, age, smoking status, disease extent, disease duration, or number of prior hospitalizations (Table 1). There was no significant difference in modified Truelove and Witts criteria on admission between patients with a shorter (< 7 days) versus longer hospital stay (≥ 7 days). A significantly greater proportion of patients with LOS ≥ 7 days were biologic therapy naïve at time of admission (60% vs. 38%, $P = 0.03$).

Table 1 Patient and disease characteristics associated with LOS ≥ 7 in patients with ASUC

	LOS < 7 Days $N=50$	LOS ≥ 7 Days $N=45$	p-value
Age, median (IQR)	36.5 (27–46)	34 (27–40)	$P=0.25$
Male gender, *n* (%)	16 (32%)	14 (31%)	$P=0.93$
Smoker, *n* (%)	4 (8)	4 (9)	$P=0.21$
Disease duration (Years), median (IQR)	5.9 (2.3–13)	3.5 (1–8.8)	$P=0.13$
Prior hospitalizations for ASUC, median (IQR)	1 (0–1)	1(0–2)	$P=0.60$
Extensive or pan-colitis, *n* (%)	35 (70)	37 (82)	$P=0.16$
Modified truelove and witts criteria, *n* (%)	Mild = 3 (6)	Mild = 1 (3)	$P=0.15$
	Moderate = 3 (6)	Moderate = 0 (0)	
	Severe = 44 (88)	Severe = 44 (97)	
Medications at time of admission:			
Mesalamine,* *n* (%)	23 (46)	17 (38)	$P=0.41$
Systemic Steroids	26 (52)	24 (53)	$P=0.89$
Immunomodulator[†]	9 (18)	7 (16)	$P=0.75$
Biologic or small molecule[‡]	20 (40)	22 (49)	$P=0.38$
Anti-TNF[§]	17 (34)	16 (36)	$P=0.87$
Opioid analgesic	10 (20)	7 (16)	$P=0.72$
Previous medication exposure:			
Mesalamine,* *n* (%)	49 (98)	42 (93)	$P=0.26$
Systemic steroids	45(90)	38 (84)	$P=0.42$
Immunomodulator[†]	19 (38)	16 (36)	$P=0.81$
Biologic or small molecule[‡]	31 (62)	27 (60)	$P=0.84$
Anti-TNF*[§]	17 (34)	7 (16)	$P=.31$
Biologic-naïve	19 (38)	18 (40)	$p=0.80$

*Mesalamine Therapy: Oral 5-ASA or Topical 5-ASA

[†]Immunomodulator: Azathioprine, Mercaptopurine, Methotrexate

[‡]Biologic or Small Molecule Therapy: Adalimumab, Golimumab, Infliximab, Vedolizumab, Tofacitinib

[§]Anti-TNF: Adalimumab, Golimumab, Infliximab

Characteristics of Hospital Management and IBD-Related Complications

For patients who had a LOS < 7 days as compared with those with LOS ≥ 7 days, there were no significant differences in admission time (morning, afternoon, evening), weekend admission, or hospitalist versus teaching care team (Table 2). Patients with LOS ≥ 7 days were more likely to have a higher maximum heart rate (median 108 vs. 97 bpm, $p=0.01$) and a higher C-reactive protein (median 65.1 vs. 51.6 mg/L vs., $P=0.05$) on admission. Maximum temperature, hemoglobin level, and ESR did not differ significantly between the groups (Table 2, $p>0.05$). Patients who tested positive for *Clostridioides difficile* ($n=11$) did not have a significantly longer LOS (8% vs. 15%, $P=0.25$). Time to flexible sigmoidoscopy was not significantly associated with LOS ($P=0.57$).

Opioid use at time of admission and median daily opioid dose were not statistically different between patients with LOS < 7 days and LOS ≥ 7 days (20% vs. 16%, $P=0.72$). However, patients who received an opioid prescription at time of discharge were more likely to have LOS ≥ 7 days (40% vs. 12%, $P=0.002$). Rates of appropriate pharmacologic venous thromboembolism (VTE) prophylaxis (Doses Received/Doses That Should Have Been Ordered) were not associated with LOS (median IQR 0.69 vs. 0.77 $P=0.82$). There was no difference in LOS in patients who underwent colectomy within 90 days after discharge compared to those who did not ($p=0.11$). There was no statistically significant difference in readmission rates at 90 days between the two groups (22% vs. 11%, $P=0.56$). There was no significant difference in LOS, colectomy rate, or time to biologic initiation before and after the implementation of the initiative ($p>0.05$), noting that LOS reduction was not the primary aim of this initiative.

Later date of in-hospital biologic therapy initiation was associated with LOS ≥ 7 days (median hospital day 4 vs. 3.5, $P=<0.001$). On multivariable logistic regression controlling for age, disease duration, disease extent, and being biologic naïve, a later hospital day of biologic therapy initiation was associated with LOS ≥ 7 (OR 3.1 95% CI 1.2–7.56, $p=0.012$) (Table 3).

Table 2 Clinical management and IBD-related complications associated with LOS ≥ 7 days in patients with ASUC

	LOS < 7 Days *N* = 50	LOS ≥ 7 Days *N* = 45	*P* value
Admission time of day, *n* (%)	M = 18 (36)	M = 11 (24)	*P* = 0.43
	A = 24 (48)	A = 27 (60)	
	E = 8 (16)	E = 7 (16)	
Weekend admission, *n* (%)	13 (26)	13 (29)	*P* = 0.75
Hospitalist team, *n* (%)	13 (26)	13 (29)	*P* = 0.75
Vitals and labs, median (IQR):			
Maximum temperature, ℃ (first 24 h)	37.2 (36.9–37.4)	37.4 (36.9–37.9)	*P* = 0.94
Maximum heart rate, bpm (first 24 h)	**97 (90–111)**	**108 (97–110)**	***P* = 0.01**
Initial C-reactive protein (mg/L)	**51.6 (15.6–90)**	**65.1 (28.9–145)**	***P* = 0.05**
Initial erythrocyte sedimentation rate (mm/hr)	43.5 (30–61)	45.5 (26–68)	*P* = 0.79
Admission hemoglobin (g/dl)	11.9 (10.4–12.9)	11.3 (9.5–12.9)	*P* = 0.25
Clostridioides difficile Positive, *n* (%)	4 (8)	7 (15)	*P* = 0.25
Hepatitis B testing prior to admission, *n* (%)	42 (84)	37 (82)	*P* = 0.82
Tuberculosis testing prior to admission, *n* (%)	38 (76)	35 (78)	*P* = 0.84
Days to inpatient flexible sigmoidoscopy, median (IQR)	2 (1–3)	2 (1–3)	*P* = 0.57
Biologic therapy administered during hospitalization, *n* (%)	**20 (40)**	**31 (69)**	***P* ≤ 0.001**
Hospital day of biologic initiation, median (IQR)	**3.5 (2–4)**	**4 (4–7)**	***P* ≤ 0.001**
Anticholinergics administered, *n* (%)	9 (18)	12 (27)	*P* = 0.30
Antidiarrheals administered, *n* (%)	2 (4)	1 (2)	*P* = 0.62
Median daily opiate dose,* median (IQR)	1.6 (0–16)	4.5 (0–32.2)	*P* = 0.24
Discharge prescription for opiates	**6 (12)**	**18 (40)**	**0.002**
Overall VTE coverage rate,* median (IQR)	0.69 (0.2–1)	0.77 (0.3–.9)	*P* = 0.82
Readmission within 90 days of discharge	11 (22)	5 (11)	*P* = 0.56

Bolded values denote statistical significant as defined by a *P*-value ≤ 0.05

*Admission time: Morning (M) 7:00 AM–3:00 PM, Afternoon (A) 3:00 PM–11:00 PM, Evening (E) 11:00 PM–7:00 AM

VTE Coverage Rate: Doses Received/Doses That Should Have Been Ordered

Median Daily Opiate Dose: oral morphine equivalents

Table 3 Multiple logistic regression of patient characteristics and clinical factors associated with LOS ≥ 7 days

	Adjusted OR	95% CI	*P*
Age	0.99	0.95–1.0	0.63
Disease Duration	0.97	0.91–1.02	0.23
Extensive colitis (E3)	1.7	0.62–5.0	0.29
Biologic naive	0.85	0.33–2.1	0.73
Hospital day of biologic initiation	**3.1**	**1.2–7.56**	**0.012**

Bolded values denote statistical significant as defined by a *P*-value ≤ 0.05

Controlling for age, disease duration, disease extent, biologic naïve

Table 4 Multiple Logistic regression of patient characteristics and clinical factors associated with LOS ≥ 7 days EXCLUDING patients who underwent colectomy during hospitalization

	Adjusted OR	95% CI	*P*
Age	0.96	0.92–1.01	0.10
Disease Duration	0.96	0.88–1.04	0.31
Extensive colitis (E3)	**4.00**	**1.04–15.34**	**0.04**
Biologic naive	**3.45**	**1.14–10.37**	**0.03**
Opiate use prior to admission	1.13	0.34–3.77	0.84
Hospital day of biologic initiation	**2.84**	**1.30–6.23**	**0.009**

Bolded values denote statistical significant as defined by a *P*-value ≤ 0.05

Controlling for age, disease duration, disease extent, biologic naïve

LOS for Non-surgical Patients

A subgroup analysis was performed excluding 15 patients who underwent colectomy during hospitalization. Patients who underwent colectomy all had LOS ≥ 7 days and were biologic therapy experienced prior to hospitalization. Multivariable analysis of our ASUC population excluding those patients who underwent colectomy (Table 4) revealed an association between being biologic naïve

and increased LOS ≥ 7 (OR 3.45, 95% CI 1.14–10.37, $p = 0.03$) as well as an association between later hospital day of biologic initiation and prolonged LOS ≥ 7 (OR 2.84, 95% CI 1.30–6.23, $P = 0.009$). Among those without colectomy, having more extensive colitis was also associated with LOS ≥ 7 (OR 4.00, CI 1.04–15.34, $p = 0.04$).

Discussion

Our study, the first to assess factors affecting prolonged LOS ≥ 7 days in a diverse ASUC population receiving treatment at a tertiary care center, found that being biologic therapy naïve, having more extensive disease, and delayed administration of inpatient biologic rescue therapy were all associated with increased LOS.

While much data exist regarding factors associated with readmission in ulcerative colitis patients [10, 15, 16], predictors of hospital LOS for patients with ASUC have not been well described. A study by Kelso et al. [17] examined factors that may predict marginally prolonged LOS (> 4 days) in a population of predominantly male veterans with all types of IBD. This study found that the majority of factors associated with longer hospitalization were markers of more severe disease. The authors hypothesized that early biologic initiation may reduce hospital length of stay.

Our data confirmed that patients with more severe ulcerative colitis are more likely to have longer hospitalization stays. These patients can be identified as those that have higher heart rate and higher CRP at time of admission, as well as those who have a greater extent of colitis. While the severity of a flare is not modifiable, early recognition of these patients could help with hospital and discharge planning and help to set expectations for patients and care teams regarding LOS. In addition, early identification of patients with severe disease who are likely to have prolonged LOS may allow for early intervention to prevent common hospital complications. Patients with prolonged hospitalizations are susceptible to numerous complications, including deconditioning, hospital acquired infections, adverse drug reactions, thrombotic events, and worsening nutritional status [18]. Approximately 10% of hospitalized patients will experience an adverse event unrelated to their underlying disease process, and risk of an adverse event increases with prolonged LOS [19]. By identifying the cohort of patients who are at higher risk to experience these complications based on their predicted LOS, we can intervene to prevent these complications by implementing interventions such as early mobilization, nutrition consults, and pharmacist intervention to prevent adverse drug reactions.

A later date of biologic initiation during hospitalization was associated with longer LOS regardless of disease extent and regardless of whether the patient ultimately underwent colectomy during hospitalization. We speculate that earlier initiation of biologic therapy would likely reduce hospital LOS. The timing of biologic therapy initiation is modifiable in both the outpatient and inpatient setting. In the outpatient setting, physicians can be more aggressive about early biologic initiation, especially given that biologic therapy has been shown to reduce the odds of hospitalization by half in UC patients [20]. Outpatient physicians can also target biologic naïve patients for earlier communication and patient education about biologic therapy to increase early patient acceptance and can begin the process of insurance authorization if needed. In the inpatient setting, addressing on the day of admission the possible need for biologic rescue therapy may be a helpful intervention to decrease time to biologic therapy initiation in the appropriate patient. Additionally, inpatient gastroenterology consultants should be very comfortable with recognizing the at-risk patient with ASUC and understanding the need for early biologic therapy.

Additionally, delays in performing required infection screening tests can delay biologic therapy initiation [16]. Prior to initiation of biologics, patients should be screened for latent tuberculosis (TB) and hepatitis B infection [21]. The need for this routine testing in the inpatient setting has been shown to be associated with longer LOS [17]. Either a TB skin test (TST) or interferon gamma release assay (IGRA) is an appropriate screening tool for latent TB, with the exception of patients with history of BCG vaccine in whom IGRA is preferred [22]. At many institutions, PPD testing is faster than IGRA as IGRA is often processed at an external laboratory, with longer turnaround time to result. We hypothesize that routine TB testing and hepatitis B testing on day of admission, or, ideally, before admission in the outpatient setting, would likely shorten LOS. Development of a protocol to expedite inpatient IGRA testing turnaround for ASUC inpatients would also likely decrease LOS. In their algorithm for the inpatient management of UC flares, Pola et al. [23] recommend performing latent TB and hepatitis B screening tests on the day of admission in anticipation of starting rescue therapy with an anti-TNF biologic or cyclosporine. Our cohort had high rates of pre-hospitalization testing for TB and hepatitis B, so we were unable to adequately address whether delays in inpatient testing were associated with increased length of stay.

There are multiple limitations of our study. The study was performed in a single tertiary care center, where healthcare utilization patterns may differ from other care settings. It has been shown that patients at tertiary centers are more likely to undergo more extensive workup and treatment as compared to community settings, which may contribute to prolonged LOS [24]. Data collection was partially retrospective, and the use of diagnosis codes may have missed eligible

hospitalizations. Retrospective data collection included those who received IV steroids for a clinical diagnosis of ASUC even without biochemical evidence of severe colitis per Truelove and Witt's criteria. These patients were included in analysis as they represent a real-world cohort of clinically diagnosed ASUC, but may not have been included in a prospective cohort. Our ASUC population had a high rate of prior biologic exposure, reflecting the tertiary care patient population. Additionally, our study has a relatively small sample size.

In conclusion, we identified both modifiable (e.g., time to biologic therapy initiation) and non-modifiable (e.g., disease severity) predictors for prolonged LOS in ASUC that may inform specific interventions aimed at reducing LOS in this population. Most notable is the importance of early biologic therapy initiation and the need to decrease barriers to timely initiation, such as with early patient education and standardized care algorithms. If patients are not responding to IV corticosteroids within 3–5 days, biologic rescue therapy must be considered without delay [2, 25]. Future studies are needed to evaluate the impact of interventions targeting modifiable predictors of LOS.

Declarations

Conflict of interest The authors have no conflict of interest to declare. All co-authors have seen and agree with the contents of the manuscript, and there is no financial interest to report.

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