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Retrospective Cohort Study

4

Older adults with acute severe ulcerative colitis have similar steroid non-response and colectomy rates as younger adults

Subhaharan D *et al.* ASUC in elderly

Abstract

BACKGROUND

There is paucity of data on outcomes of acute severe ulcerative colitis (ASUC) in older adults (≥ 60 years of age).

AIM

To assess steroid non-response rates during the index admission for ASUC in older adults. Secondary outcomes were response to medical rescue therapy and colectomy rates; at index admission, 3 and 12 mo.

METHODS

This retrospective multicentre cohort study included ASUC admissions who received intravenous steroids between January 2013 and July 2020 at two tertiary hospitals. Electronic medical records were reviewed to collect clinical, biochemical, and endoscopic data. A modified Poisson regression model was used for analysis.

RESULTS

Of 226 ASUC episodes, 45 (19.9%) occurred in patients ≥ 60 years of age. Steroid non-response rates were comparable in older adults and patients < 60 years of age [19 (42.2%) *vs* 85 (47%), $P = 0.618$, crude risk ratio (RR) = 0.89 [95% confidence interval (CI): 0.61-1.30], adjusted RR = 0.99 (0.44-2.21). Rates of response to medical rescue therapy in older adults was comparable to the younger cohort [76.5% *vs* 85.7%, $P = 0.46$, crude RR = 0.89 (0.67-1.17)]. Index admission colectomy [13.3% *vs* 10.5%, $P = 0.598$, crude RR = 1.27 (0.53-2.99), adjusted RR = 1.43 (0.34-6.06)], colectomy at 3 mo [20% *vs* 16.6%, $P = 0.66$, crude RR = 1.18 (0.61-2.3), adjusted RR = 1.31 (0.32-0.53)] and colectomy at 12 mo [20% *vs* 23.2%, $P = 0.682$, crude RR = 0.85 (0.45-1.57), adjusted RR = 1.21 (0.29-4.97)], were similar between the two groups.

CONCLUSION

In older adults with ASUC, the steroid non-response rate, response to medical rescue therapy, and colectomy rate at index admission, 3 and 12 mo is similar to patients less than 60 years of age.

Key Words: Elderly; Ulcerative colitis; Acute severe ulcerative colitis; Colectomy; Rescue therapy; Infliximab

Subhaharan D, Ramaswamy P, Willmann L, Moattar H, Bhullar M, Ishaq N, Dorrington A, Shukla D, McIvor C, Edwards J, Mohsen W. Older adults with acute severe ulcerative colitis have similar steroid non-response and colectomy rates as younger adults. *World J Gastroenterol* 2023; In press

Core Tip: This is a retrospective study to assess the outcomes of older adults (≥ 60 years of age) hospitalised with acute severe ulcerative colitis (ASUC) as per Truelove and Witts' criteria. We identified 45 episodes of ASUC in older adults and compared outcomes with 181 episodes of ASUC in patients < 60 years of age. Older adults with ASUC have similar steroid non-response rate, response to medical rescue therapy and colectomy rates up to 12 mo from index admission, when compared to patients less than 60 years of age.

8 **INTRODUCTION**

Ulcerative colitis (UC) is a chronic, relapsing-remitting, inflammatory disorder of the colon, resulting from numerous factors including genetic predisposition, environmental triggers, and gut microbiota^[1,2]. Acute severe UC (ASUC), as defined by the Truelove and Witts criteria, occurs in 10%-25% at diagnosis and 20%-30% during the disease course of UC^[3-5]. Intravenous corticosteroids (IVCS) remain the first-line therapy for ASUC, however infliximab (IFX) and ciclosporin (CsA) have been used as medical rescue therapy for those who are steroid-refractory^[6-9].

Up to 20% of patients with UC have late-onset disease with their first flare occurring after the age of 60^[10,11]. The basic principles of management of ASUC in older adults do not differ from younger patients^[12]. However, there are unique challenges in managing inflammatory bowel disease (IBD) in older adults, including delay in diagnosis, misdiagnosis, and variable clinical presentations. Older adults may suffer from comorbidities, polypharmacy, complex drug-drug interactions, cognitive dysfunction, post-surgical complications, as well as social factors, which increase complexity in management of older adults with ASUC^[13-17]. Studies have demonstrated higher treatment failure rates in elderly IBD patients who are commenced on their first anti-tumour necrosis factor agent^[18]. In the setting of these factors, management decisions need to be patient-centred and individualised to minimise morbidity and mortality for older adults with ASUC.

Advanced age has not been shown to predict outcomes in ASUC^[19]. However, in routine clinical practice, age is an important factor which is taken into consideration in the decision-making algorithm. As older adults are generally excluded from clinical trials, management decisions for these patients are often made by extrapolating data from a younger cohort of patients^[11]. Moreover, short and long-term outcomes of ASUC in this cohort of patients are not well described. The primary outcome of the study was to assess steroid non-response rates during the index admission for ASUC in older adults. The secondary outcomes were response to medical rescue therapy and colectomy rates at index admission, 3 and 12 mo.

MATERIALS AND METHODS

Study population

All consecutive admissions with a diagnosis of UC at two tertiary Australian hospitals, from January 2013 to July 2020 at Gold Coast University Hospital and from January 2018 to July 2020 at Logan Hospital, were identified using international classification of disease (ICD-10) codes (K51). Retrospective analysis identified adult patients (≥ 18 years of age) admitted for management of ASUC, as identified by Truelove and Witts

criteria^[3] (Figure 1). The study was approved by the Gold Coast Health Service Human Research Ethics Committee (Ref: LNR/2020/QGC/67173).

Inclusion was limited to patients with ASUC who received at least 3-5 d of IVCS (either hydrocortisone 400 mg/d or methylprednisolone 60 mg/d). Patients with a diagnosis of Crohn's disease or positive stool cultures for other enteric pathogens were excluded. Patients with superimposed *Clostridium difficile* or cytomegalovirus infection were included in the final analysis. Demographic, clinical and laboratory results were collected. Endoscopic data was collected from procedure reports and images, and scored based on the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) score^[20].

Therapeutic management

All patients received IVCS as per international guidelines^[21]. The Oxford criteria was used to determine failure of IVCS therapy after 3-5 d^[22]. Patients received IFX or CsA for medical rescue therapy at their treating physician's preference. The standard dose IFX induction strategy utilised was 5 mg/kg at week 0, 2 and 6. Accelerated dose of IFX was defined as 10 mg/kg on day 0 followed by 5 mg/kg at week 2 and 6. The dose of IFX was determined by the treating physician based on clinical assessment of disease severity. CsA was dosed at 2 mg/kg body weight with a target trough level of 200-300 ng/mL at 48 h. In patients responding to medical rescue therapy, maintenance therapy was based on disease severity and prior treatment history as per the treating physician's discretion.

Definitions

UC: The diagnosis of UC was based on standard clinical, endoscopic, and histological criteria^[23].

ASUC: The diagnosis of ASUC was based on Truelove and Witts criteria; defined as ≥ 6 bloody stool motions per day ⁵ and one or more of the following: Haemoglobin < 10.5

g/dL, erythrocyte sedimentation rate ≥ 30 mm/hr or C-reactive protein ≥ 30 mg/L, temperature ≥ 37.8 °C, or heart rate ≥ 90 beats/min^[3].

Disease extent: ¹ The maximum endoscopic extent at index colonoscopy according to the Montreal classification^[24]. In patients with ASUC as their first presentation of disease, the extent was determined from the first available colonoscopy after discharge, or the surgical specimen if they underwent colectomy.

Older adults with ASUC: ASUC occurring in patients ≥ 60 years of age (irrespective of the age at diagnosis of UC).

Endoscopic severity: ¹ Defined by the UCEIS. The score (0-8) is calculated by the sum of three descriptors: Vascular pattern (scored 0-2), bleeding (scored 0-3), and erosions/ulcers (scored 0-3). It is assessed at the most severely affected area on flexible sigmoidoscopy^[20].

Steroid non-response: Defined as failure to respond to IVCS as defined by the Oxford criteria^[22], and receiving either medical or surgical rescue therapy.

IFX dosing: Standard dose strategy was defined as IFX 5 mg/kg at week 0, 2 and 6. Accelerated dose was defined as IFX 10 mg/kg on day 0 followed by 5 mg/kg at week 2 and 6.

Responder to medical rescue therapy: Defined as the patient being discharged from hospital on medical therapy after receiving inpatient medical rescue therapy, and avoiding colectomy during the admission.

Outcomes

The primary outcome was to assess steroid non-response rates during the index admission for ASUC in older adults. The secondary outcomes were response to medical rescue therapy and colectomy rates at index admission, 3 and 12 mo.

Statistical analysis

Descriptive statistics were used to describe the study cohort. Results were reported as median³ with interquartile range (IQR) for continuous variables, and frequencies with percentages for categorical variables. For comparison of variables, Fisher's exact or Chi-square tests⁶ were used for categorical variables, and Wilcoxon Ranksum test for continuous variables⁷. Continuous data was tested for normality using the Shapiro-Wilk test² and a two-tailed P value of < 0.05 was considered statistically significant. A modified Poisson regression model was used to estimate risk differences (RDs) and RRs to evaluate the difference in clinical outcomes between the two groups. Kaplan-Meier plots and the Cox proportional hazards regression model were also used². A log-rank test was used to compare the curves of the Kaplan-Meier plots. Multiple imputations were performed to account for missing covariates. All analysis was performed using Stata15 (StataCorp LLC, College Station, Texas).

RESULTS

A total of 302 admissions for UC who received IVCS were identified, of which 76 were excluded. 226 episodes of ASUC were included in the analysis. 45 (19.9%) episodes of ASUC in older adults ≥ 60 years of age and 181 (80.1%) episodes in younger adults were identified (Figure 1). Median age of disease onset was 66.5 (IQR: 59-76) vs 27 (IQR: 21-37), $P < 0.001$. Disease duration was similar between the two groups (2.5 vs 2 years, P 0.94). 33 out of 45 (73.3%) episodes had their first presentation of UC after the age of 60 years. Median Charlson Comorbidity Index in older adults was 3 (IQR: 2-4). Smoking status, albumin and platelet count at admission were significantly different between the two groups. Current immunomodulator use, biologic use and oral steroid use at admission were similar between the two groups. Clinical, endoscopic, and biochemical

parameters are provided in Table 1. Summary of primary and secondary outcomes are shown in Table 2.

Primary outcome: Steroid non-response during the index admission for ASUC

Failure to IVCS therapy, as defined by the Oxford criteria^[22], was similar between older and younger adults [19 (42.2%) *vs* 85 (47%), $P = 0.618$; crude RR = 0.89 (0.61-1.30), $P = 0.34$; adjusted RR = 0.99 (0.34-2.90), $P = 0.175$; odds ratio (OR) = 0.82 (0.43-1.58), $P = 0.344$; crude hazard ratio (HR) = 0.89 (0.556-1.455), $P = 0.674$]. In older adults, of the 19 episodes that failed IVCS, 17 (89.5%) episodes received medical rescue therapy (7 episodes IFX 5 mg/kg, 4 episodes IFX 10 mg/kg, 6 episodes CsA) and 2 (10.5%) patients proceeded directly to colectomy. Median time to initiation of rescue therapy was 4 d (IQR: 3-5 d). In patients < 60 years of age, of the 85 episodes that failed IVCS, 77 (90.6%) episodes received medical rescue therapy (45 episodes IFX 5 mg/kg, 22 episodes IFX 10 mg/kg, 10 episodes CsA) and 8 (9.4%) patients underwent direct colectomy. When the cut-off age was defined as 70 years, a significantly lower proportion of episodes failed IVCS [6/23 (26.1%) in ≥ 70 years *vs* 98/203 (48.3%) in < 70 years, $P = 0.049$; crude RD = -0.22 (-0.41 to -0.03); crude RR = 0.54 (0.27-1.09), $P = 0.034$; adjusted RR = 0.36 (0.08-1.49), $P = 0.897$; crude OR = 0.378 (0.143-1.00), $P = 0.05$].

Secondary outcomes

Response to medical rescue therapy: In older adults, of the 17 episodes who received medical rescue therapy, 4 (23.5%) patients underwent colectomy during the index admission. In the younger cohort, of the 77 episodes who received medical rescue therapy, 10 (13%) patients underwent a colectomy during the index admission. The rates of response to medical rescue therapy in older adults were similar to the younger cohort [76.5% *vs* 85.7%, $P = 0.46$; crude RD = -0.092 (-0.31 to 0.12); crude RR = 0.89 (0.67-1.17), $P = 0.27$; crude OR = 0.54 (0.16-1.85)]. When the cut-off age was defined as 70 years, a lower proportion of episodes responded to medical rescue therapy [4/6 (66.7%)

in ≥ 70 years *vs* 75/88 (85.2%) in < 70 years, $P = 0.243$; crude RD = -0.18 (-0.57 to 0.19); crude RR = 0.78 (0.44-1.38); crude OR = 0.34 (0.65-1.00), $P = 0.24$].

Index admission colectomy: In older adults, 6 (13.3%) of 45 patients underwent colectomy during the index admission for ASUC compared to 19 (10.5%) of 191 patients in the younger cohort [crude RD = 0.028 (-0.08 to 0.13); crude RR = 1.27 (0.53-2.99), $P = 0.376$; adjusted RR = 1.43 (0.34-6.06), $P = 0.71$; crude OR = 1.31 (0.50-3.41); crude HR = 1.27 (0.47-3.39), $P = 0.608$]. When the cut-off age was defined as 70 years, a similar proportion of episodes underwent colectomy during the index admission [2/25 (8.7%) in ≥ 70 years *vs* 21/201 (8.7%) in < 70 years, $P = 0.52$; crude RD = -0.026 (-0.15 to 0.09); crude RR = 0.77 (0.19-3.04); adjusted RR = 0.91 (0.16-5.09), $P = 0.52$; crude OR = 0.74 (0-3.0), $P = 0.52$].

Colectomy at 3 mo: At 3 mo, 9 (20%) patients ≥ 60 years of age had undergone a colectomy, compared to 30 (17.6%) patients < 60 years of age [crude RD = -0.03 (-0.10 to 0.16); crude RR = 1.18 (0.61-2.3), $P = 0.38$; adjusted RR = 1.31 (0.32-0.53), $P = 0.82$; crude OR = 1.23 (0.54-2.80); crude HR = 1.21 (0.55-2.648, $P = 0.620$]. In older adults, of the 13 episodes which responded to medical rescue therapy, 1 patient with two episodes of ASUC within a three-month period of the index admission underwent a colectomy. When age cut-off was defined as 70 years, a lower proportion of episodes underwent colectomy at 3 mo [2/23 (8.7%) in ≥ 70 years *vs* 37/190 (19.5%) in < 70 years of age, $P = 0.264$; crude RD = -0.1.09 (-0.235 to 0.02); crude RR = 0.44 (0.11-1.73); adjusted RR = 0.72 (0.14-3.73), crude OR = 0.39 (0-1.58), $P = 0.165$].

Colectomy at 12 mo: At 12 mo, 9 (24.3%) patients ≥ 60 years of age had undergone a colectomy, compared to 42 (28.8%) patients < 60 years of age [crude RD = -0.04 (-0.20 to 0.11); crude RR = 0.85 (0.45-1.57), $P = 0.376$; adjusted RR = 1.21 (0.29-4.97), $P = 0.88$; crude OR = 0.79 (0.35-1.80); crude HR = 0.86 (0.43-1.71), $P = 0.69$]. The Kaplan-Meier curve for colectomy-free survival is shown in Figure 2. When age cut-off was defined as

70 years, a lower proportion of episodes underwent colectomy at 12 mo [2/23 (8.7%) in ≥ 70 years vs 49/203 (24.1%) in < 70 years of age, $P = 0.042$; crude RD = -0.21 (-0.35 to -0.07); crude ¹⁰RR = 0.29 (0.07-1.14), $P = 0.026$; adjusted RR = 0.63 (0.11-3.41), $P = 0.673$; OR = 0.23 (0-0.92)].

DISCUSSION

Although the management of IBD in older adults remains a challenge, the basic treatment paradigms across all age groups are the same. This study is one of the largest studies describing outcomes of ASUC in older adults. It demonstrates that the rates of steroid non-response as well as short and long-term colectomy risk in older adults is comparable to those who are less than 60 years of age.

There is an increasing number of older adults with IBD, correlating with both the rising incidence of IBD and the ageing population³^{25]}. The widely accepted definition of elderly-onset IBD is disease onset at age 60 years or older^{25]}. Hence, this study used 60 years as the cut-off age to define older adults. In this study, 20% of patients were over 60 years of age at the time of their ASUC presentation; 15% of patients (33 out of 226) had their initial diagnosis of UC after the age of 60. This is comparable to current data showing 10%-25% of IBD patients are diagnosed after the age of 60^{25,26]}. Previous studies have exhibited that older adults with UC are more likely to present with a severe initial episode, display proctocolitis or limited left-sided colitis, and develop toxic megacolon which is associated with high mortality^{27,28]}. In this study, 13 (28.9%) episodes had proctocolitis or limited left-sided colitis, and there were no episodes of toxic megacolon in older adults.

Traditionally, the Oxford index has been utilised to define steroid failure in patients with ASUC, and in this study the same definitions were applied^{22]}. Previous studies have shown that about 40% of patients with ASUC fail initial therapy with IVCS^{29]}. This study reconfirms that the rate of steroid failure is similar between older adults (42.2%) and the younger cohort of patients (47%). This is in contrast to a recently published multicentre Japanese study^{30]}. IVCS continue to be the first-line treatment option for

older adults, although steroid-specific adverse effects are to be taken into consideration. Nevertheless, older adults with ASUC should not be undertreated, as poorly controlled disease and repeated courses of steroids induce undesirable outcomes. In this study, more than 75% of older adults responded to medical rescue therapy and avoided colectomy during admission for ASUC. The effectiveness of medical rescue therapy demonstrated in the current study is comparable to that demonstrated in larger randomised-controlled trials^[31,32]. Of the episodes who responded to medical rescue therapy, only 1 patient had undergone a colectomy by 12 mo. Biologic agents in older adults with IBD were recently shown to have similar drug sustainability, effectiveness, and safety^[33]. Older adults on IFX also have a similar risk of developing adverse effects and loss of response as younger patients^[34]. Thus, medical rescue therapy can be offered judiciously to older adults.

This study has several strengths, foremost that it is one of the largest studies describing outcomes of ASUC in older adults. Although this was not a controlled trial, this cohort of patients was managed through two tertiary IBD subspecialty units which have defined treatment protocols for hospitalised ASUC patients consistent with international guidelines. Results are therefore generalisable to similar real-world clinical settings. The study has a few limitations. Firstly, the study is retrospective. Secondly, long-term safety of IFX and CsA were not studied systematically. The assessment of clinical response after initiation of rescue therapy with the Lichtiger score or Mayo score may have been beneficial. Finally, clinical and biochemical data at 12 mo may have also proved valuable for the analysis of the study.

CONCLUSION

Management of older adults with ASUC remains challenging. This study demonstrates that the rate of IVCS non-response in older adults with ASUC is similar to younger patients, and medical rescue therapy is equally effective. Clinical decisions for older adults with ASUC should still be determined by disease severity rather than chronological age alone.

ARTICLE HIGHLIGHTS

Research background

The management of older adults with acute severe ulcerative colitis (ASUC) is uniquely challenging due to their numerous medical and social factors. Up to 20% of patients with UC have late-onset disease with their first flare occurring after the age of 60.

Research motivation

There is minimal data available on the outcomes of older adults with ASUC. Previous studies report higher treatment failure rates in older adults who are commenced on their first biologic. We planned this study to define both short and long term outcomes for this cohort and determine if they have similar outcomes compared to the younger cohort.

Research objectives

We aimed to determine the steroid non-response rates for older adults with ASUC during index admission. We also aimed to study their response to medical rescue therapy and colectomy rates up to 12 mo from initial presentation.

Research methods

We conducted a retrospective cohort study investigating the short and long term outcomes among 226 ASUC episodes between January 2013 and July 2020 at two tertiary hospitals in Queensland, Australia. Clinical characteristics, laboratory parameters, and disease outcomes, including mortality, were compared between older and younger adults. A modified Poisson regression model was used for analysis.

Research results

The prevalence of older adults with ASUC was 19.9%. Steroid non-response rate in older adults were comparable to younger adults (42.2% vs 47%, $P = 0.62$). Response

rates to medical rescue therapy was also comparable between the two groups (76.5% *vs* 85.7%, $P = 0.46$). Index admission colectomy (13.3% *vs* 10.5%, $P = 0.60$), colectomy at 3 mo (20% *vs* 16.6%, $P = 0.66$), and colectomy at 12 mo (20% *vs* 23.2%, $P = 0.68$) were also similar between the two groups.

Research conclusions

Older adults with ASUC have similar outcomes compared to younger patients less than 60 years of age for rates of steroid non-response, medical rescue therapy, and colectomy at index admission, 3 and 12 mo.

Research perspectives

Clinical decisions for older adults with ASUC remains to be a challenge however should still be determined by disease severity rather than chronological age alone. Future prospective studies will allow further improvement in their management.

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