Hospitalization of Patients with Ulcerative Colitis: A Systematic Review and Meta-Analysis

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ABSTRACT Hospitalization of ulcerative colitis patients is needed in severe exacerbation of the disease or for managing complications. In this systematic review and meta-analysis the prevalence of hospitalization in ulcerative colitis and possible predictive factors are discussed. A systematic literature search of English language publications that were published before 31 December 2019 was conducted. Retrospective cohort studies describing hospitalizations of UC patients were included. Meta-analysis was performed by using comprehensive meta-analysis software. Pooled odds ratios (ORs) and 95% confidence intervals (95%CIs) were calculated for the number of patients hospitalized. Seven studies and 15 datasets were found that fulfilled the inclusion criteria. In total, the studies included 2067 patients from six countries. The event rates for the number of patients hospitalized in a follow-up duration of 42,320 patient-years and for the number of patients underwent operation in a follow-up of 24,650 patient-years were 0.065 (95%CI 0.063–0.068) and 0.019 (95%CI 0.017–0.021), respectively. More studies during the era of biologics need to be performed to identify the factors predictive of hospitalization and surgery with UC. Prevention of inflammation and UC complications may prevent hospitalization and the need for surgical treatment.

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KEY WORDS: hospitalization, inflammatory bowel disease (IBD), meta-analysis, surgery, ulcerative colitis (UC)

Hospitalization of ulcerative colitis (UC) patients is needed in cases of severe exacerbation of the disease or for managing complications. Medical therapy to suppress the inflammatory process includes 5-aminosalycilic acid, steroids, immunomodulators and biologics; however, surgery is sometimes needed for strictures or for uncontrolled inflammation. It is interesting that despite the advances in medical treatment, hospitalization rates remain high and exceeded 34% of the patients with moderate to severe disease [1-3]; however, for the total population of UC (most have mild clinical presentation) hospitalization rate is unknown. The annual cost of hospitalization for UC in United States was estimated to be US$3.4 billion [4]. The frequency of UC emergency department visits increased by 39.6% from 2006 to 2014, 2.6 times that for all-case visits [5]. However, the relative admission rate significantly decreased. Although there were lower rates of UC emergency department visits than Crohn's disease (CD), patients with UC were significantly more likely to be admitted to the hospital compared to patients with CD [5].

PATIENTS WITH ULCERATIVE COLITIS ARE HOSPITALIZED DUE TO EXACERBATION OF THEIR INFLAMMATORY DISEASE, BECAUSE OF NON-INFLAMMATORY DISEASE (SUCH AS STRICTURE OR MALIGNANCY), OR ATTRIBUTABLE TO OTHER COMPLICATIONS

Hospitalization is sometimes dangerous to the patients due to hospital-resistant bacteria, treatment and diagnostic mistakes, and even consequent depression [6]. In addition, Ananthakrishnan et al. [7] found that requiring medical hospitalization for the management of disease activity in UC is an independent predictor of the need for colectomy.

Usually, hospitalization rates in UC are expressed in number of patients per 10,000 people [8]. This expression may be confusing and misleading since the prevalence and incidence of UC may be changing over time and between different populations.

In this systematic review and meta-analysis the prevalence of hospitalization in UC and possible predictive factors are discussed. Articles that reported hospitalization rates for patient-years of follow-up or studies in which this figure could be retrieved or calculated from the results were reviewed. The procedure was implemented to overcome the obstacle of different follow-up durations in different populations.

PATIENTS AND METHODS

LITERATURE SEARCH

A systematic literature search was conducted of English language publications in MEDLINE, PubMed, Scopus, EMBASE, and CENTRAL for articles published before 31 December 2019. The following terms were used: "ulcerative colitis" AND "hospitalization". Relevant studies were screened according to established protocol. In addition, the references of reviews were screened and studies were added when appropriate [Figure 1].

INCLUSION AND EXCLUSION CRITERIA

Retrospective cohort studies describing hospitalizations of UC patients were included. The following studies were excluded: cohort studies that neither informed the number of patients hospitalized nor the duration of follow-up, reported only inflammatory bowel disease (IBD) without separate data on UC, focused on special groups of patients such as children or the elderly, or based only on administrative data. Studies were also excluded when the number of hospitalizations per patient-years of follow-up could not be calculated. PRISMA guidelines for systematic reviews were strictly followed [9]. The name of the first author, country of origin, year of the study publication, number of UC patients in the cohort, and rates of hospitalization were extracted [Table 1] [10-16].

PREDICTORS OF HOSPITALIZATION

Potential predictive factors for hospitalization were also studied, including symptoms and signs (diarrhea, constipation, abdominal pain, abdominal tenderness, weight loss, and extra intestinal manifestations), laboratory tests results (albumin, hemoglobin, iron, ferritin, CRP, ESR), endoscopic and radiology finding (severe inflammation, stricture, fistula), and treatment (steroids, immune modulator drugs, and biologics).

STATISTICAL ANALYSIS

Meta-analysis was performed by using Comprehensive Meta-Analysis Software (Version 3, Biostat Inc., Englewood, NJ, United States). Pooled odds ratios (ORs) and 95% confidence intervals (95%CIs) were calculated for the number of UC patients hospitalized and/or who underwent surgery. Heterogeneity between studies was evaluated using the Cochran *Q*-test, and it was considered to be present if the *Q*-test *P* value was less than 0.10.

Figure 1. Flow chart of the articles identified for the meta-analysis

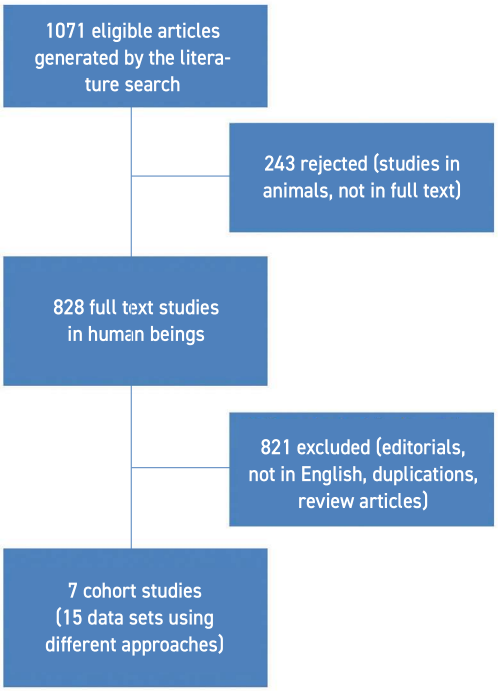
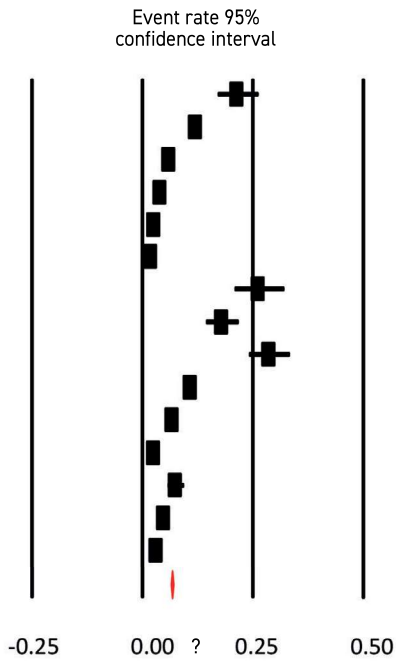


Figure 2. Meta-analysis of 7 (15 sub-studies/data sets) cohort studies looking at hospitalization in 2067 cases of ulcerative colitis in a follow-up of 42,320 patient-years

Study name	Subgroup	Event rate	*P* value
Oussalah A	UC patients, 9 years follow-up	0.213	0.000
Koh A	UC patients, 10 years follow-up	0.119	0.000
Samuel S	UC patients, 5 years follow-up	0.059	0.000
Samuel S	UC patients, 10 years follow-up	0.038	0.000
Samuel S	UC patients, 20 years follow-up	0.025	0.000
Samuel S	UC patients, 30 years follow-up	0.017	0.000
Feagan BG	UC patients without adalimumab, 1 year follow-up	0.261	0.000
Feagan BG	UC patients on adalimumab, 1 year follow-up	0.175	0.000
Golovics PA	UC patients, 1 year follow-up	0.285	0.000
Golovics PA	UC patients, 5 years follow-up	0.107	0.000
Golovics PA	UC patients, 10 years follow-up	0.066	0.000
Matsumoto S	UC patients, 14 years follow-up	0.024	0.000
Kuno T	UC patients, 5 years follow-up	0.073	0.000
Kuno T	UC patients, 10 years follow-up	0.047	0.000
Kuno T	UC patients, 20 years follow-up	0.030	0.000
		0.065	0.000



I^2 statistic was used to measure the proportion of inconsistency in individual studies. The potential publication bias using funnel plot of standard error by log odds ratio was also calculated. Even distribution of the studies denied significant publication bias.

RESULTS

During the review 1071 eligible studies were found. Of these, 243 studies were excluded because they were performed in animals and not in full text, and 821 studies were excluded because they were editorials, duplications, review articles, meta-analyses, or in a language other than English. Seven studies and 15 data-sets, including 2067 patients from six countries (USA, Canada, France, Hungary, Italy, and Japan), fulfilled the inclusion criteria [Figure 1, Table 1] [10-16]. A funnel plot demonstrates no publication bias. The event rate (ER) for the number of patients hospitalized in a follow-up duration of 42,320 patient-years was 0.065 with 95%CI 0.063–0.068 [Figure 2].

Six studies, which highlighted surgical intervention, were evaluated [Table 1]. These studies included 10 datasets and 400 patients from the same six countries. A funnel plot showed no publication bias. The ER for the number of patients who underwent surgery in a follow-up of 24,650 patient-years was 0.019 with 95%CI 0.017–0.021 [Figure 3].

SURGERY IS CONDUCTED IN 1.9% OF ULCERATIVE COLITIS HOSPITALIZATIONS

Heterogeneity (the proportion of inconsistency in individual studies) among studies was moderately significant for both hospitalization and surgery, with Q = 1440.396, df(Q) = 14, $P < 0.001$, $I^2 = 99.028\%$, and Q = 194.695, df(Q) = 3, $P < 0.001$, $I^2 = 95.377\%$, respectively.

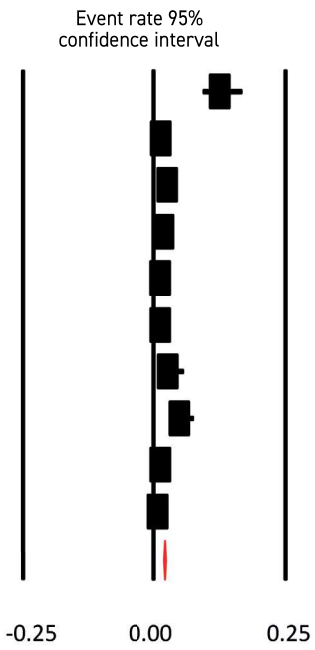
Table 1. Hospitalization in ulcerative colitis: summary of the literature

Author	Country	Year of publication	Data set Number of hospitalization for patient-years	Number of patients	Rate of hospitalization	Predictive factors
Oussalah [10]	France	2010	61 in 286.5 patient-years	191 followed 9 years	36.1% at 9 years	Predictors of hospitalization: no Clinical response after infliximab induction, infliximab indication for acute severe colitis, disease duration at infliximab initiation > 50 months, hemoglobin at infliximab initiation < 11.8 g/dl and previous treatment with methotrexate
Kohn [11]	Italy	2012	466 in 3914 patient-years	644 followed 10 years	72.4% at 10 years	Ulcerative colitis patients are 3 times more likely to be hospitalized than the general population
Samuel [12]	USA (Minnesota)	2013	193 in 11070 patient-years	369 followed 30 years	52.3% at 30 years	Steroids ER 1.8 95%CI 1.1–2.7
Feagan [13]	Canada	2014	58 in 222.3 patient-years without adalimumab 69 in 387.5 patient-years with adalimumab	963 followed 1 year	18% with and 26% without adalimumab	Protective effect of adalimumab therapy
Golovics [14]	Hungary	2014	229 in 3470 patient-years	347 followed 10 years	66% at 10 years	Extent of inflammation ER 1.79 ($P = 0.02$) Steroids therapy ER 1.98 ($P < 0.001$)
Matsumoto [15]	Japan	2014	75 in 3108 patient-years	222 followed 14 years	33.8% at 14 years	Steroid therapy ER 4.4 95%CI 1.30–14.93 Cytomegalovirus ER 8.2 95%CI 1.91–35.33
Kuno [16]	Japan	2015	139 patients total			Long extent of UC increased hospitalization
			51 hospitalizations in 685 patient-years	51 followed 5 years	37% at 5 years	
			65 hospitalizations in 1390 patient-years	65 followed 10 years	47% at 10 years	
			83 hospitalizations in 2780 patient-years	83 followed 20 years	60% at 20 years	

ER = event rate

Figure 3. Meta-analysis of 6 (10 sub-studies/data sets) cohort studies looking at surgery in 400 cases of ulcerative colitis in a follow-up of 24,650 patient-years

Study name	Subgroup	Event rate	*P* value
Oussalah A	UC patients, 9 years follow-up	0.126	0.000
Koh A	UC patients, 10 years follow-up	0.014	0.000
Samuel S	UC patients, 5 years follow-up	0.026	0.000
Samuel S	UC patients, 10 years follow-up	0.019	0.000
Samuel S	UC patients, 20 years follow-up	0.013	0.000
Feagan BG	UC patients on adalimumab, 1 year follow-up	0.013	0.000
Feagan BG	UC patients without adalimumab, 1 year follow-up	0.027	0.000
Golovics PA	UC patients, 1 year follow-up	0.049	0.000
Golovics PA	UC patients, 10 years follow-up	0.013	0.000
Matsumoto S	UC patients, 14 years follow-up	0.008	0.000



Predictive factors for hospitalization include long extent of the inflammatory process, secondary cytomegalovirus infection, hemoglobin < 11.8 g/dl, and previous treatment with steroids or methotrexate. A good response to infliximab treatment lowered the rate of hospitalization [17-19].

DISCUSSION

According to the meta-analysis, hospitalization for UC was needed in 6.5% of 42,320 patient-years, significantly lower than previously published [1-3]. Surgical treatment occurred in 1.7% of 24,650 patient-years of hospitalized patients. The main reason for hospitalization was exacerbation of the inflammation and not a surgical indication. Clinical predictive indicators for hospitalization were a result of colitis, severe inflammation, anemia, secondary cytomegalovirus infection, and previous treatment with steroids or methotrexate [20-24]. Golovics and co-authors [14] found OR of 1.79 for the extent of inflammation, similar to Kuno and colleagues [16]. Samuel et al. [12] found steroids therapy to have an OR of 1.8 for hospitalization, an observation confirmed by others [14,15]. These factors may be considered when evaluating UC patients. A good response to adalimumab and infliximab will probably prevent hospitalization or the need for surgical treatment [10,13]. Ballou et al. [5] found several significant demographic and lifestyle predictors of hospital admissions including older age, male gender, and history of smoking. These finding could not be confirmed since the included studies did not look at these parameters. Other studies reported several different epidemiological and clinical predictors for hospitalization such as female gender, need for azathioprine and anti TNF therapy [17-24].

CONCLUSIONS

More studies during the era of biologics need to be performed to identify the factors predictive of hospitalization and surgery in UC. Preventing inflammation and complications will probably lower the need for hospitalization and surgical treatment.

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Capsule

Controlling amyloid in brain and vessels

The genetic variant ε4 of the apolipoprotein E gene (*APOE*) is associated with increased risk of developing Alzheimer's disease (AD). In AD, amyloid-β forms deposits in the brain parenchyma (amyloid plaques) and in the cerebral vasculature (cerebral amyloid angiopathy, CAA). Immunotherapy targeting human APOE has reduced brain amyloid-β deposits in mice. **Xiong** et al. used a mouse model with both amyloid plaques and CAA and evaluated the effects of the anti–human APOE antibody HAE4. The treatment reduced both parenchymal amyloid-β plaques and CAA without vascular complications, whereas an antibody targeting amyloid-β exacerbated CAA-related microhemorrhages. The results suggest that HAE4 may provide therapeutic effects on amyloid removal in AD while protecting the cerebrovasculature.

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Capsule

Pathological response and survival with neoadjuvant therapy in melanoma: a pooled analysis from the International Neoadjuvant Melanoma Consortium (INMC)

The association among pathological response, recurrence-free survival (RFS) and overall survival (OS) with neoadjuvant therapy in melanoma remains unclear. **Menzies** et al. pooled data from six clinical trials of anti-PD-1-based immunotherapy or BRAF/MEK targeted therapy. In total, 192 patients were included: 141 received immunotherapy (104 combination of ipilimumab and nivolumab; 37 anti-PD-1 monotherapy) and 51 received targeted therapy. A pathological complete response (pCR) occurred in 40% of patients: 47% with targeted therapy and 33% with immunotherapy (43% combination and 20% monotherapy). pCR correlated with improved RFS (pCR 2-year 89% vs. no pCR 50%, $P < 0.001$) and OS (pCR 2-year OS 95% vs. no pCR 83%, $P = 0.027$). In patients with pCR, near pCR or partial pathological response with immunotherapy, very few relapses were seen (2-year RFS 96%), and no patient died from melanoma, whereas, even with pCR from targeted therapy, the 2-year RFS was only 79%, and OS was only 91%. Pathological response should be an early surrogate endpoint for clinical trials and a new benchmark for development and approval in melanoma.

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