

Hospitalization of Patients with Crohn's Disease: A Systematic Review and Meta-analysis

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ABSTRACT: Despite advances in therapeutic modalities, especially with biologic treatments, the number of hospitalizations due to complications for Crohn's disease did not decrease. We examined the prevalence and possible predictive factors of hospitalizations in Crohn's disease. A systematic literature search was conducted until 31 October 2018. Relevant studies were screened according to established protocol. Retrospective cohort studies describing hospitalizations of Crohn's disease 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. Twelve studies fulfilled the inclusion criteria and were comprised of 23 data-sets and included 4421 patients from six countries. A funnel plot demonstrates a moderate publication bias. We reported the event rates for the number of patients hospitalized, in a follow-up survey of 20,987 patient-years, and for the patients who underwent surgery in a follow-up of 5061 patient-years, with ORs of 0.233 with 95%CI 0.227–0.239, and 0.124 with 95%CI 0.114–0.135 ($P < 0.001$), respectively. Thus, when collecting the data from 12 cohort studies we found that hospitalization takes place in 23.3% of the patients, and operation in 12.4% along their disease duration. Patients with Crohn's disease may be hospitalized due to exacerbation of their inflammatory disease, because of non-inflammatory disease (such as fistula or stricture), or due to medical complications. The goal of therapy should be to keep the Crohn's disease patients in their natural environment and out of the hospital and to prevent surgery as much as possible.

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the number of hospitalizations due to complications did not decrease between 2003 and 2013. As a first-listed diagnosis there was a 14.5% increase in the hospitalization rate among males ($P < 0.05$) [2]. Most of the studies comparing the effect of the new biologic therapies looked at remission and response rates, but not for the possible prevention of hospitalization or surgery, since this kind of study needs a very long follow-up. Ballou et al. [3] found 48.0% increase in the frequency of Crohn's disease emergency department visits between 2006 and 2014, significantly higher than for all-case visits. But, hospitalizations for Crohn's disease decreased in 2.68%.

Most patients are treated in ambulatory facilities, but sometimes hospitalization is needed due to complications or increased inflammation not responding adequately to therapy. One way to look at hospitalization of Crohn's disease patients is as failure of a proper ambulatory treatment. Since hospitalization is expensive, inconvenient to the patient, and sometimes dangerous due to adverse events, infection with hospital resistant bacteria, and even consequent depression [4], it is very important to understand the causes for this "failure" and to characterize predictive factors for potential hospitalization that may be prevented. These factors may include socioeconomic status, smoking history, or compliance with treatment of drugs side effects (e.g., steroids, immunomodulators, and biologics) [5].

Usually hospitalization because of Crohn's disease is expressed by means of number of patients per 10,000 people in a point prevalence manner [6]. This expression may be confusing and misleading since the prevalence and incidence of Crohn's disease is changing over time and in different populations. We looked at research articles that calculated hospitalization rates or surgical treatment for patient-years of follow-up, or if this calculation was possible from the results. In this way, we overcame the obstacle of time and different populations.

In this systematic review and meta-analysis the prevalence of hospitalizations and operations in Crohn's disease, and possible predictive factors, are discussed.

METHODS

LITERATURE SEARCH

A systematic literature search was conducted of English language publications using MEDLINE, PubMed, Scopus,

Crohn's disease is a chronic disease of the intestinal tract with complex inflammatory pathology resulting in significant morbidity and mortality. It is characterized with clinical remissions and exacerbations with different level of severity leading to hospitalization and often to surgery [1,2]. Despite advances in therapeutic modalities, especially new biologic treatments,

EMBASE, and CENTRAL, up to 31 October 2018. The following terms were used: “Crohn’s disease” AND “hospitalization”. Relevant studies were screened according to established protocol. In addition, the references of reviews were screened, and studies added when appropriate [Figure 1].

INCLUSION AND EXCLUSION CRITERIA: STUDY SELECTION AND DATA EXTRACTION

Retrospective cohort studies describing hospitalizations of Crohn’s disease patients were included. The following studies were excluded: cohort studies that neither included the number of patients who were hospitalized nor the time span of the study, reported only inflammatory bowel disease (IBD) without separate data on Crohn’s disease, focused on special groups of patients such as children or the elderly, and based only on administrative data. A study was 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 [7]. The name of the first author, country of origin, year of the study publication, number of Crohn’s disease patients in the cohort, and rates of hospitalizations were extracted [Table 1] [8-19].

PREDICTORS OF HOSPITALIZATION

Potential predictive factors for hospitalization were separately studied:

- Symptoms and signs: abdominal mass, diarrhea, constipation, weight loss, abdominal tenderness, and extra intestinal manifestations
- Laboratory tests results: C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), albumin, hemoglobin, iron, ferritin
- Endoscopic and radiology finding: severe inflammation, stricture, fistula
- Treatments: steroids, immunomodulators and biologics

STATISTICAL ANALYSIS

Meta-analysis was performed by using Comprehensive Meta-Analysis Software (version 3, Biostat Inc., Englewood, NJ, USA). Pooled odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated for the number of patients hospitalized. 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. *I*² statistic was used to measure the proportion of inconsistency in individual studies. We also calculated a potential publication bias using funnel plot of standard error by log odds ratio. Even distribution of the studies denied significant publication bias.

RESULTS

We found 1192 eligible studies; 273 studies were rejected because they were performed in animals and not in full text and 907 studies were excluded due to being editorials, duplications, review articles, meta-analysis, or not in English. Twelve studies and 23 data-sets were left, including 4421

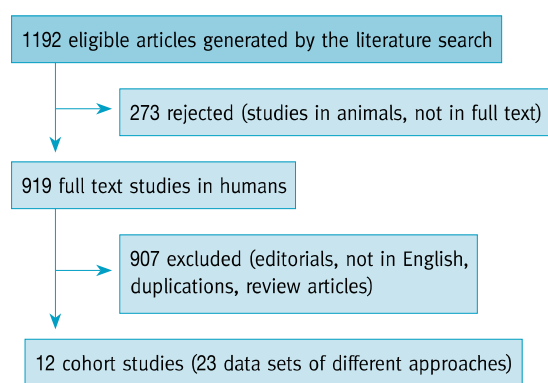
Some 12.4% of Crohn’s disease patients undergo surgeries for their disease

patients from six countries (USA, Canada, Japan, China, Brazil, and Hungary), which fulfilled the inclusion criteria and were published by 31 October 2018 [Figure 1] [Table 1] [8-19]. Funnel plot demonstrates a moderate publication bias. Looking for surgical intervention, five studies were included with nine data-sets, 498 patients from five countries (USA, Canada, China, Brazil, and Hungary) [Figure 1, Table 1] [9,10,12,13,16].

The event rates for the number of patients hospitalized in a follow-up of 20,987 patient-years and for the patients underwent surgery in a follow-up of 5061 patient-years were 0.233 with 95%CI 0.227–0.239 (*P* < 0.001), and 0.124 with 95%CI 0.114–0.135 (*P* < 0.001), respectively [Figure 2, Figure 3]. Heterogeneity (the proportion of inconsistency in individual studies) between studies was moderately significant for both, hospitalization and surgery, with *Q* = 1163.330, *df*(*Q*) = 22, *P* < 0.001, *I*² = 98.109%, and *Q* = 289.483, *df*(*Q*) = 8, *P* < 0.001, *I*² = 97.236%, respectively.

Predictive factors for hospitalization were: low vitamin D in the serum, American African origin, young age, female gender, short illness duration, non-inflammatory disease, peri-anal disease, change in the disease behavior, metabolic syndrome, involvement of the upper gastrointestinal tract, abdominal mass, fever, high absolute basophiles and lymphocytes count, and elevated CRP [8-19]. Protective effect against hospitalization was demonstrated in patients treated with adalimumab, infliximab, budesonide, and enteral nutrition of more than 900 Kcal/day [9,11,12,17].

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



DISCUSSION

Efficient and safe treatment, which minimizes the number of hospitalizations and surgery, is the goal of the physician who

Table 1. Hospitalization in Crohn's disease: 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
De Boer Visser	Canada	1990	13 Crohn's disease patients in 44.8 patient-years	112 Crohn's disease	11.6% in 3 months	Abdominal mass, body temperature, absolute basophil and lymphocyte counts, aspartate aminotransferase and blood urea nitrogen serum levels, and place of residence
Feagan	USA	2008	35 Crohn's disease patients after a year adalimumab treatment 40 Crohn's disease patients after a year placebo treatment	517 Crohn's disease patient on adalimumab and 261 patients on placebo for 1 year	6.8% of the patients treated with adalimumab 15.5% of the patients on placebo	Adalimumab therapy prevented hospitalization
Chow	China (Hong Kong)	2009	26 Crohn's disease patients with involvement of the upper gastrointestinal tract in 90 patients-year 50 Crohn's disease patients without involvement of the upper gastrointestinal tract in 306 patients-year	30 with patients with involvement of the upper gastrointestinal tract 102 patients without involvement of the upper gastrointestinal tract	86.9% of the patients with involvement of the upper GI Tract 49.3% of the patients without involvement of the upper gastrointestinal tract	Involvement of the upper gastrointestinal tract is a risk factor for hospitalization
Watanabe	Japan	2010	81 Crohn's disease patients with ileal involvement on enteral nutrition > 900 Kcal/d in 1479 patient-years 82 Crohn's disease patients with ileal involvement on enteral nutrition < 900 Kcal/d in 1006 patient-years	135 on enteral nutrition > 900 Kcal/d 102 on enteral nutrition < 900 Kcal/d	60% in the enteral nutrition > 900 Kcal/d 80% in the enteral nutrition < 900 Kcal/d	Enteral nutrition > 900 Kcal/d in Crohn's disease patients with ileal involvement prevented hospitalization
Leombruno	Canada	2011	338 infliximab treated in 676 patient-years 670 non-infliximab treated in 1340 patient-years	414 infliximab group 7281 non-infliximab group	34.0% in the infliximab treated group at 2 years 40.7% in the non-infliximab group at 2 years, <i>P</i> = 0.010	Infliximab therapy prevented hospitalizations
de Souza	Brazil	2013	72 sub-occlusive ileocecal Crohn's disease patients randomized for azathioprine or mesalamine	36 in each group followed 3 years	61.1% in the azathioprine group and 83% in the mesalamine group	Azathioprine better than mesalamine
Click	USA (Pennsylvania)	2015	351 Crohn's disease asymptomatic patients 59 in 702 patient-years	351 followed 2 years	16.8% at 2 years	Elevated CRP 33.3% hospitalized vs. 12.8%, <i>P</i> < 0.0001 OR 2.2, 95%CI 1.13–3.98
Fitzmorris	USA (Alabama)	2015	868 Crohn's disease patients 293.5 in 1000 patient-years Metabolic syndrome 369.9 in 1000 patient-years 290.4 in 1000 patient-years	868 followed 4 years	NA	Twice in metabolic syndrome
Golovics	Hungary	2015	331 Crohn's disease patients 178 hospitalizations in 1655 patient-years	333 followed 5 years	53.7% at 5 years	OR for non-inflammatory disease 1.32, perianal disease 1.47, change in disease behavior 2.38, need for steroids 3.14, need for immunosuppressive 2.08, need for surgery 7.25
Orr	USA (Alabama)	2016	924 hospitalization in 3012 patient-years: no budesonide 68 hospitalizations in 263 patient-years: budesonide 1–90 days 89 hospitalizations in 457 patient-years: budesonide > 90 days	767 (664 – no budesonide, 45 1–90 days, 58 > 90 days)	OR for budesonide (1–90 days) 0.85, 95%CI 0.65–1.10, for budesonide > 90 days 0.71, 95%CI 0.56–0.91	Budesonide treatment prevented hospitalization
Walker	USA (Alabama)	2017	801 hospitalizations in 3476 patient-years of Caucasian American 345 hospitalizations in 872 patient-years of African American	909 (702 Caucasians, 207 African-Americans)	Caucasian American: 230.4/1000 person-years African American: 395.6/1000 person-years	African American, young, women, lower duration of Crohn's disease increased hospitalization
Venkata	USA (Alabama)	2017	271 hospitalizations in 898 patient-years with low vitamin D 101 hospitalization in 712 patient-years with normal vitamin D	196 Crohn's disease patients with vitamin D level measured	OR for lower vitamin D 1.44, 95%CI 1.11–1.87	Low vitamin D level in the serum increased hospitalization

treats chronic diseases, and Crohn's disease is just an example for this statement. As long as the Crohn's disease patient is in clinical remission, managing normal life with acceptable

quality of life, hospitalization is prevented. Needless to say, hospitalization of Crohn's disease patient is expensive and may end with complications such as infection and sepsis.

Figure 2. Meta-analysis of 12 (23 sub-studies/data-sets) cohort studies looking at hospitalization in 4421 cases of Crohn's disease in a follow-up of 20987 patient-years

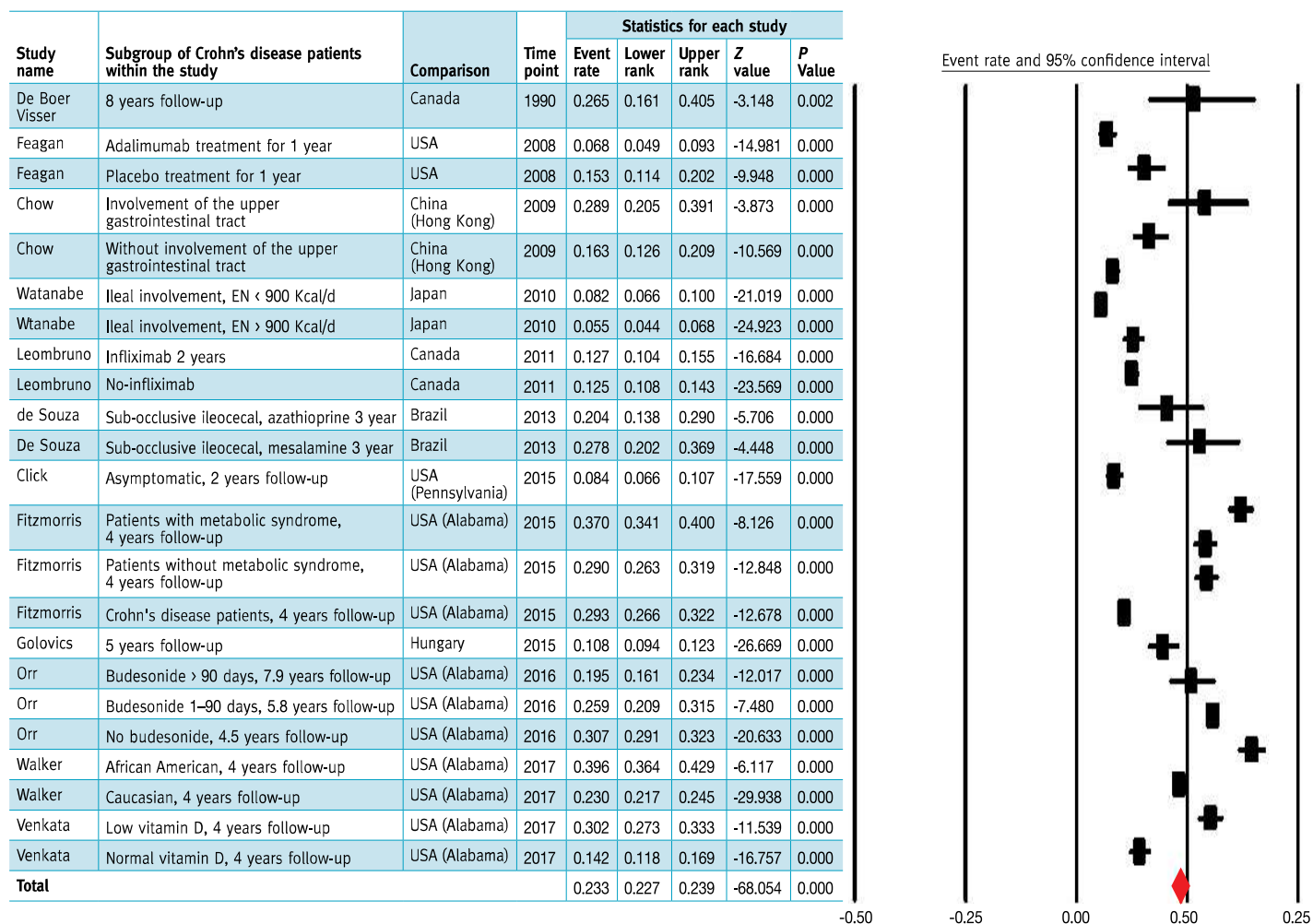
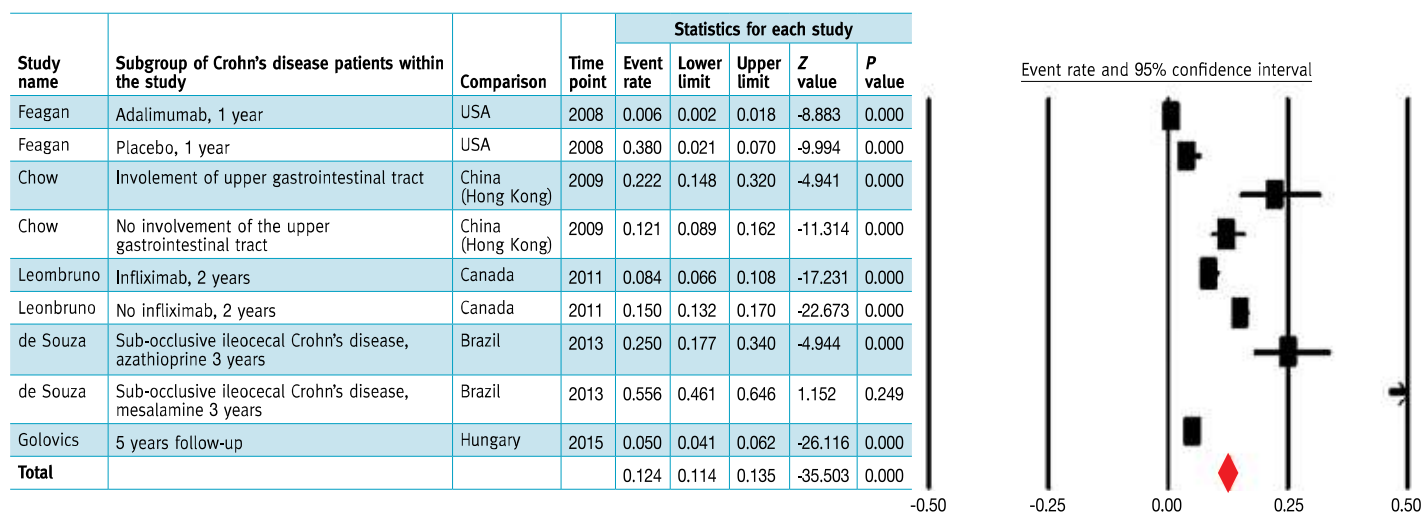


Figure 3. Meta-analysis of 5 (9 sub-studies/data-sets) cohort studies looking at surgery in 498 cases of Crohn's disease in a follow-up of 5061 patient-years



Based on the data from 12 cohort studies we found that 23.3% of the patients were hospitalized, and 12.4% underwent surgery during their disease duration. Patients with Crohn's disease may be hospitalized due to exacerbation of their inflammatory disease, because of non-inflammatory disease (such as fistula or stricture), or other complications.

The main predictive factors collected from the included articles are due to the inflammatory disease, and may be prevented [Table 1]. Epidemiological and clinical factors such as race (e.g., American non-white), short illness duration, young age at diagnosis, female gender, or involvement of the upper gastrointestinal tract; clinical signs and symptoms such as abdominal mass, fever, peri-anal disease, or fistula; and laboratory factors such as elevated CRP, low vitamin D in the serum, or high absolute basophiles and lymphocytes count. Awareness of the physician to these factors may direct more intense and directed therapy and prevent hospitalization. Factors that prevent hospitalization were also described, such as therapy with adalimumab or infliximab or enteral nutrition of more than 900 Kcal. Orr et al. [17] found a decrease of 29% of hospitalization rate in patients who were treated with budesonide for more than 90 days. Leombruno and co-authors [12] found that patients who received infliximab had a significantly lower risk of experiencing a Crohn's disease related intra abdominal surgery (HR = 0.64; 95%CI 0.51–0.81) or hospitalization (HR = 0.73; 95%CI 0.63–0.85). Infliximab users also experienced lower rates of hospitalized days (RR = 0.69; 95%CI 0.49–0.97). Similar findings described by Feagan and colleagues [9] who found a decrease of 8.7% in hospitalization rate for patients treated with adalimumab. Thus, medication compliance seems to be very important in preventing hospitalization and surgery.

LIMITATIONS

The limitation of our study is in the moderate heterogeneity between the studies, the different populations involved, changing treatment approach, and attitudes toward the new biologics and surgery in Crohn's disease. In addition, cigarette smoking, upper respiratory or enteric infections, nonsteroidal anti-inflammatory drugs, and possibly stress, might initiate and exacerbate symptoms and lead to hospitalizations, but these situations had not been measured in the included studies [3,20,21].

CONCLUSIONS

Our findings describe predictive factors for hospitalization of Crohn's disease patients. Hospitalization may be due to exacerbation of their inflammatory disease, because of non-inflammatory disease, or as a result of medical complications. The aim of disease management should be to keep patients in their natural environment and out of the hospital, and to prevent surgery as much as possible.

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