International Journal of Colorectal Disease (2021) 36:831–840
https://doi.org/10.1007/s00384-021-03876-z

ORIGINAL ARTICLE

Long-term cost and complications of surgery in patients with ulcerative colitis: a claims data analysis

M. Ghiani[1] · D. Naessens[2] · P. Takacs[3] · D. Myers[4] · B. Bokemeyer[5] · T. Wilke[6]

Accepted: 31 January 2021 / Published online: 10 February 2021

Abstract

Objectives Use claims data to assess healthcare resource utilization (HCRU) and cost for patients with ulcerative colitis (UC) who had surgery and patients who did not.

Methods UC patients from a German health insurance were included between 01/01/2010–31/12/2017. Patients with proctocolectomy or colectomy between 01/07/2010 and 31/12/2014 were identified, and surgery date was set as index. For patients with IPAA, the last surgery in the 6 months was taken as index. Non-surgery patients received random index. After propensity score matching, UC-related HCRU and cost were observed for three years post-index.

Results Of 21,392 UC patients, 85 underwent surgery and 2655 did not. After matching, 76 were included in the surgery group and 114 in the non-surgery group. Matched cohorts did not differ in baseline characteristics and mortality rates where high in both groups (21.1% and 29.0%, respectively). The percentage of patients with at least one hospitalization in the follow-up period was higher in the surgery (53.9%) compared to the non-surgery group (25.4%, $p<0.001$). In contrast, the number of outpatient prescriptions of UC-related drugs in the non-surgery group (11.2) was almost twice as large as in the surgery group (5.8, $p<0.001$). Hospitalization cost was 4.6 times higher in the surgery (1955.5€) than in the non-surgery group (419.6€, $p<0.001$). Medication cost was three times higher in the non-surgery group (6519€) compared to the surgery group (2151.7€, $p<0.001$).

Conclusions Based on hospitalizations, outpatient visits, and medical treatment, results show a considerable patient burden in UC from surgery complications or disease exacerbation in case of colectomy.

Keywords Inflammatory bowel disease (IBD) · Ulcerative colitis (UC) · Surgery · Costs · Healthcare resource utilization (HCRU) · Crohn's disease (CD)

Introduction

The prevalence of ulcerative colitis (UC) is as high as around 300 (US) to 500 (Europe) cases per 100,000 people [1], and UC incidence was reported to be increasing in newly industrialized countries [1, 2]. UC is associated with a high patient burden [3] and can become a life-threatening condition in presence of colonic and systemic complications or due to the development of colorectal cancer [4]. Thus, understanding the best course of treatment represents a public health priority and affects different aspects like the clinical picture as well as psychosocial impairments [5]. In addition, understanding the burden associated with different treatment options is crucial to evaluate the cost-effectiveness of new interventions.

Traditionally, surgical options entailing the removal of the entire colon and rectum (proctocolectomy) are considered curative [6–8], and approximately 20% of UC patients undergo surgery during the course of their disease [9]. Previous work has documented good long-term health outcomes among patients who receive proctocolectomy with ileal pouch anal anastomosis (IPAA) [7, 9, 10]. However, a number of studies have shown that IPAA is associated with high postoperative complications [11–17], and surgery is in general associated

✉ M. Ghiani
Marco.Ghiani@ipam-wismar.de

1 IPAM e.V., Alter Holzhafen 19, 23966 Wismar, Germany
2 Janssen Pharmaceutica, Beerse, NV, Belgium
3 Janssen Global Commercial Strategic Organization Hungary, Budapest, Hungary
4 Janssen Global Commercial Strategic Organization, Stockholm, Sweden
5 Gastroenterology Practice, Minden, Germany
6 Ingress-Health HWM GmbH, Wismar, Germany

with frequent complications such as wound infection, intra-abdominal abscess, small bowel obstruction, ileostomy-related complications, and hemorrhage [18]. Moreover, patients undergoing surgery for UC typically have an increased risk of thromboembolic events, although this is also found in UC patients with severe clinical activity [19–21]. In line with that, a longitudinal study using data from a hospital in Canada showed that adjusted costs were higher for patients who underwent colectomy compared to medically responsive patients [22]. However, there is a lack of reliable and recent data on surgery-related complications HCRU and costs in UC patients, and most of the evidence comes from single-center studies, which are plagued with selection bias [23].

Hence, this work aimed to assess UC-related healthcare resource utilization (HCRU) and cost in health claims data and compare patients who had surgery with patients who received exclusively medical treatment, adjusting for demographic characteristics, disease severity, and treatment history.

Methods

Study population

This work retrospectively analyzed health claims data provided by a German statutory health insurance, AOK PLUS, including over 3.3 million insured lives in the regions of Saxony and Thuringia. The dataset included patient-level information on demographic characteristics (age, gender, and date of death), outpatient and inpatient treatment (date of outpatient/inpatient treatment, specialty of the outpatient physician, ICD-10 diagnosis codes, inpatient procedures and operations, and outpatient prescriptions), and costs (inpatient care costs, and cost of outpatient prescriptions). Clinical information on severity of disease and laboratory values were not available in the data.

All adult patients with at least one inpatient or two confirmed outpatient UC diagnoses (ICD-10: K51) between 01/01/2010 and 31/12/2017 (study period) were identified. Patients who received only outpatient UC diagnoses and at least one concomitant inpatient diagnosis of Crohn's disease (CD; ICD-10: K50) were excluded to conservatively identify UC patients. Inpatient surgeries were documented using German OPS codes (operations and procedures key), which are the German modification of the International Classification of Procedures in Medicine (ICPM) and the official classification of inpatient and outpatient procedures in Germany. Patients who had a hospitalization associated to colectomy or proctocolectomy (OPS: 5-456) after first UC diagnosis and between 01/07/2010 and 31/12/2014 (inclusion period) were included in the study population (surgery group). The date of surgery hospitalization was set as index. For patients who underwent ileal pouch anal anastomosis (IPAA) and had multiple surgeries within six months, the date of the last surgery was set as index, as IPAA is often carried out in two or three steps. For patients who never had a hospitalization for colectomy or proctocolectomy during the study period (non-surgery group) a random index date was assigned within the inclusion period and after first observed UC diagnosis [24, 25]. Non-surgery patients without a prescription of corticosteroids (ATC codes: H02, A07EA) or biologics (ATC codes: L04AA33, L04AB02, L04AB04, L04AB06, L04AA23, and L04AC05) in the six months before index were dropped to enhance comparability with the surgery patients, who are typically prescribed corticosteroids or biologics before resorting to surgery [26]. Moreover, for inclusion in the non-surgery group, it was required that no aid prescription for a stoma bag (product group code in German claims: 29.26) was made during the study period. Lastly, to ensure that complete information was obtained, all patients were required to have at least 6 months of continuous enrollment in the insurance plan prior to index date and at least 3 years of continuous enrollment after index. Death of patients after a first observed UC diagnosis was the only exception and led to censoring.

Statistical analysis

Patients in the surgery group were matched to comparable patients in the non-surgery group using a 1 : 2 nearest-neighbor propensity score matching (PSM) with replacement and maximum caliper 0.01. The propensity score was estimated using a logistic regression model for a binary indicator of whether the patient underwent surgery (yes/no). The covariates included age at index date, gender, the Charlson comorbidity index (CCI) excluding age factor in the six months before index, the number of inpatient and outpatient visits in the baseline period, a categorical measure of level of care received by the patient, binary indicators for inpatient/outpatient diagnoses of literature-based UC-related extra-intestinal complications [27], an indicator for an inpatient/outpatient diagnosis of CD, and treatment history (including binary indicators for the prescription of corticosteroids, immunosuppressants, biologics, and other UC-related medications). A detailed description of all the variables included in the PSM logistic regression is provided in Supplemental Table 1. For all UC patients observed in the sample, as well as for matched and unmatched cohorts, descriptive statistics were reported for baseline characteristics, mortality, and length of follow-up since index date.

For each patient, the following outcomes were collected for the three years after index date: (1) number of UC-related hospitalizations per-patient-year (PPY), overall and by diagnosis, and excluding the surgery hospitalization for patients in the surgery group; (2) number of UC-related visits to a general physician (GP) or a specialist PPY, overall and by diagnosis; (3) number of outpatient prescriptions of UC-related medications PPY; (4) cost of UC-related hospitalizations PPY (based on DRG reimbursement codes), overall and by diagnosis, and excluding the cost of the surgery hospitalization for patients in the surgery group; and (5) cost of UC-related medications PPY (pharmacy sales price at prescription date, as documented in the database), overall and by quarter after index. Supplemental Table 2 and Supplemental Table 3 report the list of ICD-10/OPS and ATC codes used to identify, respectively, UC-related inpatient/outpatient visits and outpatient prescriptions.

All reported variables for patient characteristics, treatment, HCRU and costs were analyzed using descriptive statistics. Differences between surgery and non-surgery patients in average baseline characteristics and follow-up HCRU and costs were tested for statistical significance using *t*-tests. *t*-tests were based on unweighted (before matching) and weighted (with matching weights for matched cohorts) regression models of the variables on an indicator for surgery. In addition, for baseline characteristics, the percentage bias was assessed before and after matching. This was defined as the percentage difference of the sample means in the surgery and non-surgery subsamples as a percentage of the square root of the average of the sample variances in the surgery and non-surgery groups [28]. Density functions for the number of outpatient prescriptions per patient year were estimated using a kernel density estimator. Differences in estimated densities between surgery and non-surgery groups were tested for statistical significance using a Kolmogorov–Smirnov equality-of-distributions test. In all analyses, statistical significance was defined as *P*-value lower than 0.05. All analyses were performed using Stata (Version 14.1) and MS-SQL (Version 17.9.1). As this work was a non-interventional retrospective study based on anonymized data, informed consent of patients was not required, in accordance with German laws and the policies of the institutions assessing patient-level data (IPAM and AOK PLUS). The study was based on a protocol approved before start of data analysis by a scientific committee including all authors.

Results

Between 01/01/2010 and 31/12/2017, 21,392 patients received at least one inpatient or two confirmed outpatient diagnoses of UC. Of these, 592 patients were excluded due to having received only outpatient UC diagnoses and at least one inpatient CD diagnosis, 8 were dropped due to having proctocolectomy or colectomy before the inclusion period, 69 because they had their first surgery after the inclusion period, 3 due to undergoing proctocolectomy or colectomy before their first observed UC diagnosis, 4966 due to having their first UC diagnosis after the inclusion period, 62 died before the start of the inclusion period, and 3 had CD as diagnosis associated to proctocolectomy or colectomy (misdiagnosis prior to surgery). Of the remaining 15,689 patients, 15,601 never had proctocolectomy between 01/01/2010 and 31/12/2017 (non-surgery group), and 88 had their first UC-related surgery between 01/07/2010 and 31/12/2014 (surgery group). In the non-surgery group, 12,821 patients were excluded because they did not receive at least one prescription of corticosteroids and/or biologics in the six months before index date. Eighty-seven patients were dropped overall due to not meeting the continuous insurance requirement, and 41 were dropped due to being younger than 18 at index. In the end, the surgery group had 85 patients and the non-surgery group 2655 patients. Figure 1 reports the attrition chart for patient selection.

The unmatched cohorts displayed substantial unbalance in baseline characteristics (Table 1, Panel A): patients in the surgery group were significantly younger, less likely to be females, had on average more inpatient and outpatient visits in the six months before index, and were more likely to have a manifestation of UC in the dermatologic and oral system. In addition, compared to patients in the non-surgery group, patients in the surgery group were less likely to have received corticosteroids or antimicrobials, and more likely to have received immunosuppressants, biologics, or antipropulsives.

A logistic regression of an indicator of surgery on baseline characteristics was employed to estimate the propensity score (Supplemental Figure 1), that is the probability of surgery conditional on observable baseline characteristics. The *c*-statistic of the estimated model was 0.9, indicating a strong predictive ability. Matching patients in the surgery group to at most two patients in the non-surgery group based on their estimated propensity score, the matched cohorts included 76 patients who underwent surgery and 114 patients who did not. Based on a comparison of their baseline characteristics (Table 1, Panel B), there was no residual unbalance. Matched cohorts were also similar in terms of length of follow-up (Supplemental Table 4) and mortality was high in both the surgery and non-surgery groups (21.1% vs 30.3%, p=0.196). Of the 76 patients who underwent surgery, 34 had proctocolectomy (28 open surgical, 6 laparoscopic), 37 had colectomies (27 open surgical, 10 laparoscopic), 2 had other procedures.

Healthcare resource utilization

Table 2 reports comparisons of the matched cohorts in terms of UC-related hospitalizations and outpatient visits. While no difference was found in the number of outpatient visits with UC-related diagnosis between the two cohorts, significant differences were found for hospitalizations. The percentage of patients with at least one hospitalization in the follow-up period (excluding the index hospitalization in the surgery-group)

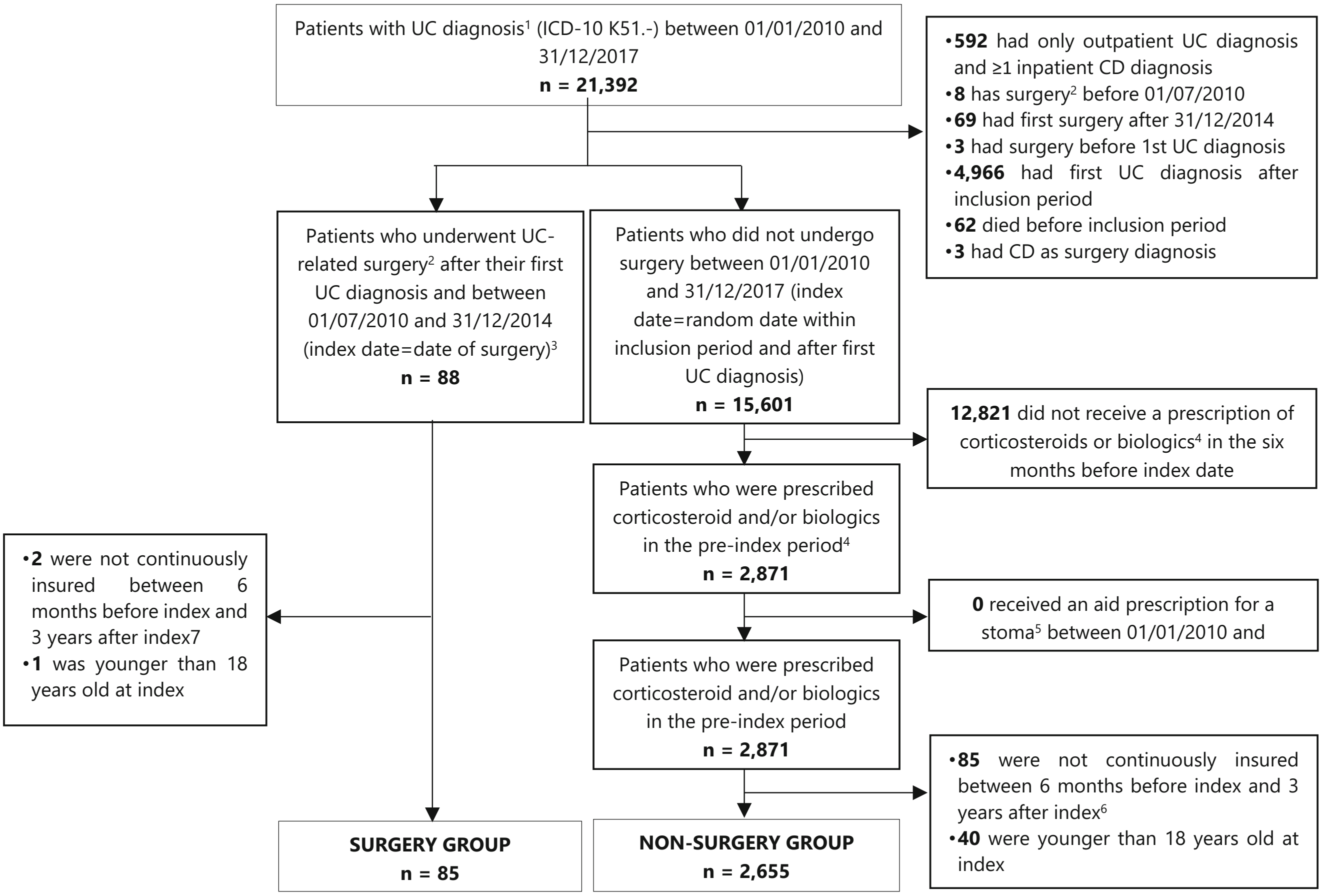

Fig. 1 Attrition chart for patient selection. (1) At least one inpatient main diagnosis, or two confirmed outpatient diagnoses. (2) proctocolectomy or colectomy (OPS codes: 5-456.-). (3) Thirty-two patients had proctocolectomy or colectomy with IPAA (OPS codes: 5-456.01, 5-456.03, 5-456.05, 5-456.11, 5-456.13, 5-456.15, 5-456.21, 5-456.23, 5-456.25, 5-456.x1, 5-456.x3, 5-456.x5). Of these, 3 patients underwent two surgeries with OPS code 5-456.- within a 6-month period. No patient underwent multiple surgeries with OPS code 5-456.- within a period of seven or more months. (4) ATC code for corticosteroids: H02, A07EA (oral administration). ATC codes for biologics: L04AA33, L04AB02, L04AB04, L04AB06, L04AA23, L04AC05. (5) GKV product group: 29.26-. (6) With the exception of death, which leads to censoring. Grace period of 30 days allowed

was significantly higher in the surgery group (53.9%) compared to the non-surgery group (25.4%, p<0.001). Specifically, 32.9% of the patients in the surgery group had at least one hospitalization with UC as main diagnosis during the follow-up period, compared to the 13.2% in the non-surgery group (p=0.004). Similarly, 36.8% of the surgery patients had at least one subsequent hospitalization with other UC-related diagnoses compared to 15.8% in the non-surgery group (p=0.003). As shown in Supplemental Figure 2, the most prevalent hospitalization diagnoses in the surgery group, other than UC, were colorectal cancer (9.2% compared to 1.8% in the non-surgery group), manifestations of UC in the dermatological and oral system (9.2% vs 4.4% in the non-surgery group), abscess (7.9% vs 0.9%), and stricture (5.3% vs 0.9%). In addition, a number of diagnoses occurred only in the surgery group: fistulae (3.9%), thromboembolic events (1.3%), manifestations of UC in the hepatopancreatobiliary system (2.6%), revision of a stoma (6.6%), and endorectal vacuum therapy for the treatment of anastomotic leak (1.3%). Furthermore, in the surgery group, the number of hospitalizations per patient year (0.4) and the total number of hospitalization days per patient year (3.9) were higher compared to the non-surgery group (0.2 and 1.5, respectively).

In contrast, patients who did not undergo surgery were found to rely more on drugs compared to surgery patients. As reported in Table 3, the number of outpatient prescriptions of any UC-related drug in the non-surgery group (11.2) was almost twice as large as in the surgery group (5.8; p<0.001). The most frequently prescribed medications PPY in the non-surgery group were aminosalicylates (2.6), biologics (1.9), analgesics (1.7), immunosuppressants (1.5), and systemic corticosteroids (1.1). In contrast, in the surgery group, patients relied more on analgesics (2.1), and antipropulsives (1.1), while only 0.4 prescriptions of biologics and 0.3 prescriptions of systemic steroids PPY were observed. When investigating the estimated densities of the number of prescriptions

Table 1 Balance of baseline characteristics in unmatched and matched cohorts

Variable	Surgery	Non-surgery group	% bias	% reduction bias	*P*-value
Panel A: unmatched cohorts	***N*=85**	***N*=2655**			
Age at index	53.024	58.985	−33.200	-	**0.004**
Female	0.400	0.550	−30.200	-	**0.006**
CCI	2.941	2.647	9.700	-	0.374
Number of inpatient visits	2.012	0.571	125.300	-	**<0.001**
Number of outpatient visits	9.529	8.510	20.400	-	0.050
Level of care ≥1	0.024	0.072	−22.700	-	0.088
Musculoskeletal manifestation	0.059	0.049	4.500	-	0.667
Dermatologic and oral manifestation	0.200	0.106	26.200	-	**0.006**
Hepatopancreatobiliary manifestation	0.141	0.091	15.600	-	0.118
Ocular manifestation	0.047	0.064	−7.500	-	0.520
Crohn's disease	0.247	0.173	18.100	-	0.078
Use of aminosalicylates	0.635	0.615	4.200	-	0.701
Use of systemic corticosteroids	0.459	0.718	−54.500	-	**<0.001**
Use of local corticosteroids	0.176	0.330	−35.700	-	**0.003**
Use of immunosuppressants	0.282	0.145	34.000	-	**<0.001**
Use of biologics	0.271	0.062	58.200	-	**<0.001**
Use of antipropulsives	0.129	0.036	34.200	-	**<0.001**
Use of antibiotics	0.082	0.102	−6.900	-	0.547
Use of antimicrobials	0.035	0.026	5.600	-	0.580
Use of anti-inflammatory and antirheumatic	0.141	0.237	−24.600	-	**0.040**
Use of analgesics	0.329	0.315	3.200	-	0.771
Number of other agents	4.859	5.035	−4.100	-	0.715
Length of follow-up	2.578	2.399	16.9	-	0.258
Mortality	0.211	0.289	−18.2	-	0.225
Panel B: matched cohorts	***N*=76**	***N*=114**			
Age at index	52.908	56.263	−18.700	43.700	0.254
Female	0.395	0.329	13.300	56.000	0.402
CCI	2.987	3.276	−9.600	1.600	0.584
Number of inpatient visits	1.895	2.276	−33.200	73.500	0.195
Number of outpatient visits	9.118	9.954	−16.700	18.000	0.313
Level of care ≥1	0.026	0.026	0.000	100.000	1.000
Musculoskeletal manifestation	0.066	0.092	−11.600	−157.100	0.551
Dermatologic and oral manifestation	0.184	0.243	−16.500	36.900	0.377
Hepatopancreatobiliary manifestation	0.132	0.138	−2.100	86.800	0.906
Ocular manifestation	0.053	0.053	0.000	100.000	1.000
Crohn's disease	0.263	0.191	17.800	1.900	0.290
Use of aminosalicylates	0.632	0.586	9.500	−123.500	0.564
Use of systemic corticosteroids	0.513	0.579	−13.800	74.600	0.419
Use of local corticosteroids	0.184	0.184	0.000	100.000	1.000
Use of immunosuppressants	0.289	0.257	8.100	76.100	0.652
Use of biologics	0.263	0.270	−1.800	96.800	0.928
Use of antipropulsives	0.105	0.092	4.800	85.900	0.787
Use of antibiotics	0.079	0.112	−11.300	−63.700	0.493
Use of antimicrobials	0.039	0.053	−7.600	−35.900	0.701
Use of anti-inflammatory and antirheumatic	0.118	0.178	−15.200	38.200	0.307
Use of analgesics	0.329	0.263	14.000	−341.200	0.378
Number of other agents	4.882	5.480	−13.900	−240.500	0.414
Length of follow-up	2.578	2.375	19.2	−13.2	0.245
Mortality	0.211	0.303	−21.2	−16.7	0.196

Boldface denotes significance at the 0.05 confidence level. The % bias is the % difference of the sample means in the treated and non-treated sub-samples as a percentage of the square root of the average of the sample variances in the treated and non-treated groups (formulae from Rosenbaum and Rubin, 1985).

(irrespective of dose or number of tablets or vials) of UC-related medications overall (Supplemental Figure 3) and by medication group (Supplemental Figure 4), the Kolmogorov Smirnov test rejected the null hypothesis of equal distribution for any medication ($p<0.001$), aminosalicylates ($p<0.001$), systemic corticosteroids ($p<0.001$), immunosuppressants ($p<0.001$), biologics ($p=0.05$), and anti-inflammatory drugs ($p=0.04$). As reported in the figures, patients in the surgery group exhibit a higher probability to receive no drug prescriptions or lower numbers of prescriptions compared to patients who did not undergo surgery.

Table 2 Comparison of UC-related inpatient and outpatient visits in the matched cohorts

	Matched surgery patients (*N* = 76)	Matched non-surgery patients (*N* = 114)	*P*-value
Hospitalizations			
At least one hospitalization (%)	53.947	25.439	**<0.001**
UC diagnosis	32.895	13.158	**0.004**
Other diagnosis	36.842	15.132	**0.002**
Number of hospitalizations PPY	0.378	0.170	**0.004**
UC diagnosis	0.127	0.062	**0.032**
Other diagnosis	0.251	0.111	**0.028**
Total number of hospitalization days PPY	3.945	1.544	**0.006**
UC diagnosis	1.373	0.541	**0.027**
Other diagnosis	2.700	0.996	**0.035**
Outpatient visits			
Number of outpatient visits PPY	7.247	7.108	0.880
Number of outpatient visits by a general practitioner PPY	3.557	3.146	0.301
Number of outpatient visits by a specialist PPY	3.690	3.963	0.697

Index hospitalization excluded for patients who underwent surgery. Boldface denotes significance at the 5% significance level

Costs

Table 4 compares hospitalization and medication costs PPY in the two matched cohorts. While overall costs were higher for patients in the non-surgery group (8237.0€) compared to the surgery group (3335.8€, p=0.003), hospitalization costs excluding the surgery hospitalization at index were almost five times higher for patients who underwent surgery (1955.5€) compared to patients who did not (419.6€, p<0.001). Medication costs were driven by biologics, which were three times higher for patients who did not undergo surgery (6519€) compared to patients in the surgery group (2151.7€, p<0.001).

When analyzing the percentage of patients treated with biologics by quarter after index (Fig. 2), the percentage of patients in the surgery group who received at least one biologic prescription in the last quarter of follow-up (7.8%) was three times higher compared to the first quarter (2.6%). In comparison, the percentage of non-surgery patients with at least one biologic prescription in the last quarter of follow-up (23.5%) was 1.6 times higher compared to the first quarter (14.9%), while reaching a maximum of 29.2% at the seventh quarter after index. Similarly, the cost of biologics per patient month among patients with at least one prescription raised in the surgery group from 333.5€ in the first quarter after index to 1503.6€ in the last quarter of follow-up. In comparison, costs for biologics in the non-surgery group were similar in the first (1583.3€) and last (1657.8€) quarters of follow-up. While costs were significantly higher for the non-surgery group throughout the follow-up period, they were not statistically different in the two groups during the last quarter.

Discussion

Using German claims data over the period 2010–2017, this paper found evidence that UC patients who underwent colectomy or proctocolectomy were more likely to experience long-term complications and incur subsequent UC-related hospitalizations compared to a propensity score matched cohort of UC patients who relied exclusively on medical treatment. This resulted in significantly higher hospitalization costs for patients who underwent surgery compared to patients who relied only on medications. Moreover, although patients in the non-surgery group had on average higher costs for biologics during follow-up, these costs were increasing over time for patients in the surgery group and, in the last quarter of follow-up, biologic costs were similar in the two groups. The increase in cost of biologics for surgery patients reflected an increasing need for biologic treatment for patients who underwent surgery, possibly also linked to pouchitis after IPAA.

While previous studies highlighted the relevance of inpatient costs for UC patients using hospital data [22, 29], this work is novel in that it uses claims data (which are free of study site and patient selection bias) to document HCRU and cost patterns related to long-term UC complications in patients who underwent surgery compared to patients who did not. Specifically, 54% of the surgery patients were found to have at least one UC-related hospitalization after surgery, compared to 25% of patients who did not have surgery. This gap was driven by patients experiencing complications of the index surgery (revision of a stoma and endorectal vacuum therapy

Table 3 Comparison of UC-related outpatient prescriptions in the matched cohorts

	Matched surgery patients (*N* = 76)	Matched non-surgery patients (*N* = 114)	*P*-value
Number of prescriptions per patient year			
Any UC-related medication	5.775	11.163	**<0.001**
Aminosalicylates	0.542	2.593	**<0.001**
Systemic corticosteroids	0.3445	1.143	**<0.001**
Local corticosteroids	0.413	0.741	0.201
Immunosuppressants	0.031	1.563	**<0.001**
Biologics	0.363	1.924	**0.001**
Antipropulsives	1.102	0.333	**0.037**
Antibiotics	0.197	0.208	0.858
Antimicrobials	0.031	0.060	0.388
Antiinflammatory	0.579	0.590	0.955
Analgesics	2.143	1.724	0.474

Boldface denotes significance at the 5% significance level

for the treatment of anastomotic leak), as well as exacerbations of the disease such as fistula, abscess, stricture, colorectal cancer, and extra-intestinal manifestations in the dermatological, oral or hepatopancreatobiliary systems. Of the 7 surgery patients with colorectal cancer, 5 had received colectomy and 2 proctocolectomy. Prior or concomitant use of immunosuppressants is unlikely to have increased complications rates in the surgery group more than in the non-surgery group, as patients were matched based on baseline use of immunosuppressants and non-surgery patients used immunosuppressants more than surgery patients during the follow-up period (Table 3).

Patients who did not undergo surgery were shown to rely more on biologics compared to surgery patients. However, the prevalence of patients who were prescribed biologics after surgery tripled over a 3-year follow-up, suggesting that patients experienced disease activity after surgery and an increasing need for treatment over time. As a result of these differences, inpatient healthcare costs were higher among patients who underwent surgery. Medication costs (driven by biologics) were higher among non-surgery patients, with a cost-increasing trend in the surgery group. While cost of biologics was significantly higher in the non-surgery group throughout the follow-up period, at the end of follow-up, they were similar in the two groups, suggesting that they relied on medical treatment in a comparable amount. As such, this study points out how real-world surgical procedures in UC may be associated with unintended long-term consequences, which may also result in higher costs for patients.

The findings of this study are in line with previous work showing that UC surgery is associated with high postoperative complications and frequent complications [11–16, 18]. Few studies investigated resource use and costs associated to UC-related surgery [23]. A Swiss longitudinal study of IBD patients reported that, between 2006 and 2016, costs for UC patients increased by 10% each year due to rising pharmaceutical costs [30]. Similarly, a survey of Dutch IBD patients suggested that healthcare costs are mainly driven by medication costs [31, 32]. On the other hand, a retrospective longitudinal study of UC patients in Canada highlighted the

Table 4 Comparison of UC-related hospitalization and medication costs (€) in matched cohorts

	Matched surgery patients (*N* = 76)	Matched non-surgery patients (*N* = 114)	*P*-value
Hospitalization costs PPY (€)	1955.5	419.6	**<0.001**
UC	1136.4	226.4	**<0.001**
Other	2041.5	309.3	**<0.001**
Medication costs PPY (€)	1380.4	7817.4	**<0.001**
Biologics	2151.7	6519.9	**<0.001**
Other	536.8	1031.1	**<0.001**
Hospitalization + medication costs PPY (€)	3335.8	8237.0	**0.003**

Index hospitalization excluded for patients who underwent surgery. Boldface denotes significance at the 5% significance level

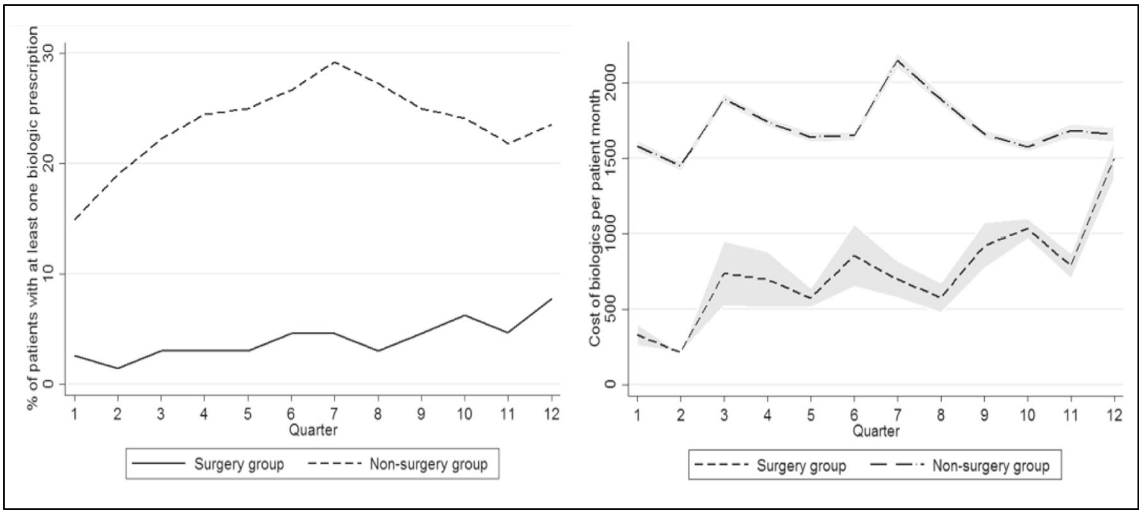

Fig. 2 Use and cost of biologics after index date. For each quarter after index date, the graph on the left reports the percentage of patients who received at least one biologic in that quarter, as a percentage of patients alive at the end of the quarter. The graph on the right, reports cost of biologics per patient month in each quarter after index, among patients with at least one prescription in that quarter

relevance of surgical costs, showing that UC mean daily costs between 2005 and 2018 were lower compared to 1998 and 2004 due to decreases in colectomies and other gastrointestinal hospitalization costs [29]. Similarly, a longitudinal study using data from an hospital in Canada showed that adjusted costs were higher for patients who underwent colectomy compared to medically responsive patients [22].

The results of this study present several weaknesses. Although indications for surgery and medical treatment are different, PSM enhanced comparability of cohorts achieving balance in terms of observable baseline characteristics. However, residual unobservable factors may be biasing the results. Under the assumption that observable characteristics proxy for unobservable factors, the bias due to selection on non-observables is minor. In addition, small sample sizes prevented subgroup analyses by type of surgery. Patients included in the study underwent different procedures, including colectomy, which is not recommended by guidelines for UC patients. While this is in line with the aim of describing patients' outcomes in real-world clinical practice, more research is warranted to investigate costs and HCRU in patients who underwent total proctocolectomy with IPAA. Furthermore, the data did not provide information on laboratory results, cost of outpatient physicians, clinical data on disease activity and patients' well-being and psychosocial impairments. Potential medical interventions received by patients, such as participation in clinical trials, and interventions that do not qualify for medical claims were also not captured in the analysis. No information was available on whether the treating center was high or low volume in UC surgery, which may impact the performance of surgery. Lastly, data from AOK PLUS represent approximately 5% of the German population insured by statutory health insurance and are geographically restricted to Saxony and Thuringia, which may produce regional bias. However, as the German system is characterized by uniform healthcare regulations and access to health resources, this bias is assumed to be small.

Conclusions

While we do not make recommendations against surgery, this paper provides evidence of a considerable patient burden in UC following surgery, resulting from complications and possible pouch problems or exacerbation of the disease in cases of colectomy. Surgery patients were found to rely significantly more on inpatient treatment than non-surgery patients and had an increasing need for medical treatment over time. These long-term unintended consequences of surgery are reflective of real-world standard of care practices, which may deviate from guidelines and included the use of colectomy. This is important both for UC treatment decisions and for evaluation of the cost-effectiveness of new interventions and surgery for UC.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00384-021-03876-z.

Author contribution Conception and design of the study: all

Acquisition of data: M-G.

Analysis of data: M.G.

Interpretation of data: all

Drafting the article: M.G., T.W.

Review and finalization of the article: all

All authors have made substantial contributions to the study and writing of the article and have given their final approval of the version to be submitted.

Funding This study was supported by Janssen Pharmaceutica.

Data Availability Due to German data protection law (SGB X), we are not allowed to distribute the analyzed dataset.

Declarations

Ethics and scientific approval and consent to participate Because the present study was non-interventional, had a retrospective design, and was based on anonymized data, informed consent of patients was not required. This is in accordance with German law and policies of the institutions assessing patient-level data (IPAM, and AOK PLUS). The study was evaluated by a scientific steering committee to which all the authors belonged and was based on a study protocol approved before start of data analysis.

Conflict of interest Marco Ghiani participated in this study as a staff member of IPAM; the work of IPAM in this study was financed by Janssen Pharmaceutica. Dominik Naessens, Peter Takacs, and David Myers are employees of Janssen. Ulf Maywald is an employee of AOK PLUS and reports Honoria from Roche and MSD. Thomas Wilke and Bernd Bokemeyer have received honoraria from several pharmaceutical companies, e.g., Novo Nordisk, Abbvie, Merck, GSK, Astra Zeneca, Bayer, Boehringer Ingelheim, and Pharmerit

References

1. Ng SC, Shi HY, Hamidi N, Underwood FE, Tang W, Benchimol EI, Panaccione R, Ghosh S, Wu JCY, Chan FKL, Sung JJY, Kaplan GG (2017) Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. Lancet 390:2769–2778
2. Kaplan GG, Ng SC (2017) Understanding and preventing the global increase of inflammatory bowel disease. Gastroenterology 152: 313–321.e2
3. Lindsay JO, Armuzzi A, Gisbert JP, Bokemeyer B, Peyrin-Biroulet L, Nguyen GC, Smyth M, Patel H (2017) Indicators of suboptimal tumor necrosis factor antagonist therapy in inflammatory bowel disease. Dig Liver Dis 49:1086–1091
4. Gallo G, Kotze PG, Spinelli A (2018) Surgery in ulcerative colitis: when? How? Best practice & research. Clin Gastroenterol 32-33: 71–78
5. Petruo VA, Krauss E, Kleist A, Hardt J, Hake K, Peirano J, Krause T, Ehehalt R, von Arnauld de la Perriére P, Büning J, Treml O, Krauss N, Albrecht H, Felten G, Hermannspahn U, Burkhardt U, Eisold M, Teich N, Siegmund B, Maaser C, Bokemeyer B, Baumgart DC, Neurath MF, Mudter J, German IBD Study Group (GISG) KND (2019) Stresswahrnehmung, Persönlichkeitsmerkmale, psychosoziale Beeinträchtigungen und Bewältigungsstrategien bei Patienten mit chronisch-entzündlichen Darmerkrankungen. Z Gastroenterol 57:473–483
6. Bohl JL, Sobba K (2015) Indications and options for surgery in ulcerative colitis. Surg Clin North Am 95:1211–1232 vi
7. Devaraj B, Kaiser AM (2015) Surgical management of ulcerative colitis in the era of biologicals. Inflamm Bowel Dis 21:208–220
8. Bennis M, Tiret E (2012) Surgical management of ulcerative colitis. Langenbeck's Arch Surg 397:11–17
9. Kühn F, Klar E (2015) Surgical principles in the treatment of ulcerative colitis. Viszeralmedizin 31:246–250
10. Mark-Christensen A, Erichsen R, Brandsborg S, Rosenberg J, Qvist N, Thorlacius-Ussing O, Hillingsø J, Pachler JH, Christiansen EG, Laurberg S (2018) Long-term risk of cancer following ileal pouch-anal anastomosis for ulcerative colitis. J Crohns Colitis 12:57–62
11. Fazio VW, Kiran RP, Remzi FH, Coffey JC, Heneghan HM, Kirat HT, Manilich E, Shen B, Martin ST (2013) Ileal pouch anal anastomosis: analysis of outcome and quality of life in 3707 patients. Ann Surg 257:679–685
12. Øresland T, Bemelman WA, Sampietro GM, Spinelli A, Windsor A, Ferrante M, Marteau P, Zmora O, Kotze PG, Espin-Basany E, Tiret E, Sica G, Panis Y, Faerden AE, Biancone L, Angriman I, Serclova Z, de Buck van Overstraeten A, Gionchetti P, Stassen L, Warusavitarne J, Adamina M, Dignass A, Eliakim R, Magro F, D'Hoore A, European Crohn's and Colitis Organisation (ECCO) (2015) European evidence based consensus on surgery for ulcerative colitis. J Crohns Colitis 9:4–25
13. de Zeeuw S, Ahmed Ali U, Ali UA, Donders RART, Hueting WE, Keus F et al (2012) Update of complications and functional outcome of the ileo-pouch anal anastomosis: overview of evidence and meta-analysis of 96 observational studies. Int J Color Dis 27:843–853
14. Weston-Petrides GK, Lovegrove RE, Tilney HS, Heriot AG, Nicholls RJ, Mortensen NJM et al (2008) Comparison of outcomes after restorative proctocolectomy with or without defunctioning ileostomy. Arch Surg 143:406–412
15. de Montbrun SL, Johnson PM (2009) Proximal diversion at the time of ileal pouch-anal anastomosis for ulcerative colitis: current practices of North American colorectal surgeons. Dis Colon Rectum 52:1178–1183
16. Kiely JM, Fazio VW, Remzi FH, Shen B, Kiran RP (2012) Pelvic sepsis after IPAA adversely affects function of the pouch and quality of life. Dis Colon Rectum 55:387–392
17. Andersson P, Norblad R, Söderholm JD, Myrelid P (2014) Ileorectal anastomosis in comparison with ileal pouch anal anastomosis in reconstructive surgery for ulcerative colitis–a single institution experience. J Crohns Colitis 8:582–589
18. Teeuwen PHE, Stommel MWJ, Bremers AJA, van der Wilt GJ, de Jong DJ, Bleichrodt RP (2009) Colectomy in patients with acute colitis: a systematic review. J Gastrointest Surg 13:676–686
19. Merrill A, Millham F (2012) Increased risk of postoperative deep vein thrombosis and pulmonary embolism in patients with inflammatory bowel disease: a study of National Surgical Quality Improvement Program patients. Arch Surg 147:120–124
20. Bernstein CN, Blanchard JF, Houston DS, Wajda A (2001) The incidence of deep venous thrombosis and pulmonary embolism among patients with inflammatory bowel disease: a population-based cohort study. Thromb Haemost 85:430–434
21. Wallaert JB, de Martino RR, Marsicovetere PS, Goodney PP, Finlayson SRG, Murray JJ, Holubar SD (2012) Venous thromboembolism after surgery for inflammatory bowel disease: are there modifiable risk factors? Data from ACS NSQIP. Dis Colon Rectum 55:1138–1144
22. Coward S, Heitman SJ, Clement F, Hubbard J, Proulx M-C, Zimmer S, Panaccione R, Seow C, Leung Y, Datta N, Ghosh S, Myers RP, Swain M, Kaplan GG (2015) Ulcerative colitis-associated hospitalization costs: a population-based study. Can J Gastroenterol Hepatol 29:357–362
23. Lindsay JO, Bergman A, Patel AS, Alesso SM, Peyrin-Biroulet L (2015) Systematic review: the financial burden of surgical complications in patients with ulcerative colitis. Aliment Pharmacol Ther 41:1066–1078
24. Reed NS, Altan A, Deal JA, Yeh C, Kravetz AD, Wallhagen M, Lin FR (2018) Trends in health care costs and utilization associated with untreated hearing loss over 10 years. JAMA Otolaryngol Head Neck Surg 145(1):27–34. Chicago
25. Chen J-H, Lan J-L, Cheng C-F, Liang W-M, Lin H-Y, Tsay GJ, Yeh WT, Pan WH (2015) Effect of urate-lowering therapy on all-

cause and cardiovascular mortality in hyperuricemic patients without gout: a case-matched cohort study. PLoS One 10:e0145193

26. Magro F, Gionchetti P, Eliakim R, Ardizzone S, Armuzzi A, Barreiro-de Acosta M, Burisch J, Gecse KB, Hart AL, Hindryckx P, Langner C, Limdi JK, Pellino G, Zagórowicz E, Raine T, Harbord M, Rieder F, for the European Crohn's and Colitis Organisation [ECCO] (2017) Third European Evidence-based consensus on diagnosis and management of ulcerative colitis. Part 1: definitions, diagnosis, extra-intestinal manifestations, pregnancy, cancer surveillance, surgery, and ileo-anal pouch disorders. J Crohns Colitis 11:649–670
27. Levine JS, Burakoff R (2011) Extraintestinal manifestations of inflammatory bowel disease. Gastroenterol Hepatol 7:235–241
28. Rosenbaum PR, Rubin DB (1985) Constructing a control group using multivariate matched sampling methods that incorporate the propensity score. Am Stat 39:33
29. Dan A, Boutros M, Nedjar H, Kopylov U, Afif W, Khalil MA, Rahme E (2017) Cost of ulcerative colitis in Quebec, Canada: a retrospective cohort study. Inflamm Bowel Dis 23:1262–1271
30. Pillai N, Dusheiko M, Maillard MH, Rogler G, Brüngger B, Bähler C, Pittet VEH, Swiss IBD Cohort Study Group, Anderegg C, Bauerfeind P, Beglinger C, Begré S, Belli D, Bengoa JM, Biedermann L, Bigler B, Binek J, Blattmann M, Boehm S, Borovicka J, Braegger CP, Brunner N, Bühr P, Burnand B, Burri E, Buyse S, Cremer M, Criblez DH, de Saussure P, Degen L, Delarive J, Doerig C, Dora B, Dorta G, Egger M, Ehmann T, el-Wafa A, Engelmann M, Ezri J, Felley C, Fliegner M, Fournier N, Fraga M, Frei P, Frei R, Fried M, Froehlich F, Funk C, Furlano RI, Gallot-Lavallée S, Geyer M, Girardin M, Golay D, Grandinetti T, Gysi B, Haack H, Haarer J, Helbling B, Hengstler P, Herzog D, Hess C, Heyland K, Hinterleitner T, Hiroz P, Hirschi C, Hruz P, Iwata R, Jost R, Juillerat P, Keller C, Knellwolf C, Knoblauch C, Köhler H, Koller R, Krieger-Grübel C, Ublick GK, Künzler P, Landolt M, Lange R, Lehmann FS, Macpherson A, Maerten P, Maillard MH, Manser C, Manz M, Marbet U, Marx G, Matter C, Meier R, Mendanova M, Michetti P, Misselwitz B, Morell B, Mosler P, Mottet C, Müller C, Müller P, Müllhaupt B, Münger-Beyeler C, Musso L, Nagy A, Neagu M, Nichita C, Niess J, Nydegger A, Obialo N, Oneta C, Oropesa C, Peter U, Peternac D, Petit LM, Gfeller FP, Pilz JB, Pittet V, Raschle N, Rentsch R, Restellini S, Richterich JP, Rihs S, Ritz MA, Roduit J, Rogler D, Rogler G, Rossel JB, Rueger V, Saner G, Sauter B, Sawatzki M, Schäppi M, Scharl M, Scharl S, Schelling M, Schibli S, Schlauri H, Uebelhart SS, Schnegg JF, Schoepfer A, Seibold F, Seirafi M, Semadeni GM, Semela D, Senning A, Sidler M, Sokollik C, Spalinger J, Spangenberger H, Stadler P, Steuerwald M, Straumann A, Funk BS, Sulz M, Suter A, Thorens J, Tiedemann S, Tutuian R, Vavricka S, Viani F, Vögtlin J, Känel RV, Vonlaufen A, Vouillamoz D, Vulliamy R, Wermuth J, Werner H, Wiesel P, Wiest R, Wylie T, Zeitz J, Zimmermann D (2019) The evolution of health care utilisation and costs for inflammatory bowel disease over ten years. J Crohns Colitis 13:744–754
31. van der Valk ME, Mangen M-JJ, Leenders M, Dijkstra G, van Bodegraven AA, Fidder HH, de Jong DJ, Pierik M, van der Woude CJ, Romberg-Camps MJL, Clemens CHM, Jansen JM, Mahmmod N, van de Meeberg PC, van der Meulen-de Jong AE, Ponsioen CY, Bolwerk CJM, Vermeijden JR, Siersema PD, van Oijen MGH, Oldenburg B, on behalf of the COIN study group and the Dutch Initiative on Crohn and Colitis (2014) Healthcare costs of inflammatory bowel disease have shifted from hospitalisation and surgery towards anti-TNFα therapy: results from the COIN study. Gut 63:72–79
32. Bokemeyer B, Hardt J, Hüppe D, Prenzler A, Conrad S, Düffelmeyer M, Hartmann P, Hoffstadt M, Klugmann T, Schmidt C, Weismüller J, Mittendorf T, Raspe H (2013) Clinical status, psychosocial impairments, medical treatment and health care costs for patients with inflammatory bowel disease (IBD) in Germany: an online IBD registry. J Crohns Colitis 7:355–368