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Observational Study

Intestinal complications in Brazilian patients with ulcerative colitis treated with conventional therapy between 2011 and 2020

Adalberto Lima Martins, Rodrigo Galhardi Gasparini, Ligia Yukie Sasaki, Rogerio Saad-Hossne, Alessandra Mileni Versut Ritter, Tania Biatti Barreto, Taciana Marcolino, Claudia Yang Santos

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Abstract**BACKGROUND**

This was an observational, descriptive, and retrospective study from 2011 to 2020 from the Department of Informatics of the Brazilian Healthcare System database.

AIM

To describe the intestinal complications (IC) of patients with ulcerative colitis (UC) who started conventional therapies in Brazil's public Healthcare system.

METHODS

Patients ≥ 18 years of age who had at least one claim related to UC 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) code and at least 2 claims for conventional therapies were included. IC was defined as at least one claim of: UC-related hospitalization, procedures code for rectum or intestinal surgeries, and/or associated disease defined by ICD-10 codes (malignant neoplasia of colon, stenosis, hemorrhage, ulcer and other rectum or anus disease, megacolon, functional diarrhea volvulus, intussusception and erythema nodosum). Descriptive statistics, annual incidence, and

incidence rate (IR) [per 100 patient-years (PY)] over the available follow-up period were calculated.

RESULTS

In total, 41229 UC patients were included (median age, 48 years; 65% women) and the median (interquartile range) follow-up period was 3.3 (1.8-5.3) years. Conventional therapy used during follow-up period included: mesalazine (87%), sulfasalazine (15%), azathioprine (16%) or methotrexate (1%) with a median duration of 1.9 (0.8-4.0) years. Overall IR of IC was 3.2 cases per 100 PY. Among the IC claims, 54% were related to associated diseases, 20% to procedures and 26% to hospitalizations. The overall annual incidence of IC was 2.9%, 2.6% and 2.5% in the first, second and third year after the first claim for therapy (index date), respectively. Over the first 3 years, the annual IR of UC-related hospitalizations ranged from 0.8% to 1.1%; associated diseases from 0.9% to 1.2% - in which anus or rectum disease, and malignant neoplasia of colon were the most frequently reported; and procedure events from 0.6% to 0.7%, being intestinal resection and polyp removal the most frequent ones.

CONCLUSION

Study shows that UC patients under conventional therapy seem to present progression of disease developing some IC, which may have a negative impact on patients and the burden on the health system.

Key Words: Ulcerative colitis; Brazil; Conventional therapy; Intestinal complications; Real world; Public healthcare

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Core Tip: This population-based study investigated intestinal complications (ICs) in patients with ulcerative colitis (UC) undergoing therapy available in the public healthcare system (Sistema Único de Saúde) of Brazil over the last decade. Our results showed that some patients with UC undergoing conventional therapy, seem to present an active and progressive disease and develop relevant ICs, which demand important resources of the healthcare system and have a negative impact on their lives.

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INTRODUCTION

Ulcerative Colitis (UC) is an idiopathic inflammatory disease of the mucosa and colon that commonly involve colonic regions both proximal to and distal from the site of the primary lesion[1]. The typical presentation includes symptoms such as bloody diarrhea, rectal urgency, and abdominal pain[2]. UC is a component of inflammatory bowel diseases (IBD), which are chronic, immune-mediated inflammatory diseases of the gastrointestinal tract. The etiopathogenesis is multifactorial involving different environmental, genetic, immune-mediated and intestinal microbial factors[3].

Although epidemiological studies are still scarce in developing countries, the incidence and prevalence of UC is increasing worldwide, along with IBD[4]. A systematic review showed that the incidence and prevalence of UC in Latin America varied between regions and studies, ranging from 0.04 to 8.00/100000 and 0.23 to 76.1/100000, respectively, and generally increased over the period from 1986 to 2015[5].

Many patients have long periods of complete remission, but the cumulative probability of remaining relapse-free for two years is only 20%, decreasing to less than 5% in 10 years[6]. Chronic inflammation of the colorectal mucosa, as is typically found in UC, is a proven risk factor for neoplasm of colon. The development of neoplasm of colon in patients with UC is related to several factors: Duration, extent, activity, severity and family history of the disease. The progression from UC inflammation to neoplasm and/or surgery is a multi-step process in which the accumulation of symptoms and sequential mucosal changes gradually transition to a low-grade change to neoplasm[7]. Indications for emergency surgery include refractory toxic megacolon, perforation, and ongoing severe colorectal bleeding[8].

UC is a progressive disease that can lead to other serious complications and/or even life-threatening complications. One of the most common UC disease progressions are: anorectal dysfunction (50%)[9], proximal extension (25%) with the greatest proximal extension occurring during the first 10 years[10, 11], pseudopolyposis (16%)[12] and other such as impaired permeability in remission or with mucosal healing, stenosis and dysmotility[10]. Thus, complications related to UC represent a substantial burden in terms of costs and patient quality of life, with hospital admissions, operations and treatments being the most relevant burdens[13].

The treatment of UC currently aims to monitor indicators of disease activity and to adjust therapy, aiming to achieve clinical remission and prevent long-term complications, such as dysplasia, colorectal cancer, hospitalizations and colectomy[14]. In 2021, the STRIDE-II study confirmed STRIDE-I's long-term goals of clinical remission, histological remission, and endoscopic mucosal healing[15] and added absence of disability, restoration of quality of life, and normal growth in children. Symptomatic relief and normalization of serum and fecal markers were determined as short-term targets[16].

Treatment will vary depending on the severity and location of the UC. For proctitis, topical therapy with 5-aminosalicylic acid (5-ASA) compounds is used. For more severe UC, oral and local 5-ASA compounds and corticosteroids are indicated to induce remission. For patients who do not respond to these treatments, intravenous steroids are used. When refractory to this, calcineurin inhibitors (cyclosporine, tacrolimus), tumor necrosis factor- α antibodies or immunomodulators are then used[17].

For patients with moderate to severe UC, drugs such as thiopurines and biologics are indicated to control symptoms and heal the intestinal mucosa. Anti-tumor necrotizing factor (TNF) drugs include infliximab, adalimumab and golimumab. Of the anti-integrin drug, vedolizumab can be mentioned. And the anti-p40 antibody targeting interleukin (IL)-12 and IL-23, we can mention ustekinumab and small molecules (Janus Kinase inhibitor - tofacitinib)[18]. Biologics were not available in the public healthcare system during the study period in Brazil. Studies have observed an association between the administration of biologics therapies such as anti-TNF- α within the first 2 years of diagnosis and several beneficial effects, including reduction risk of intestinal surgery[4,5,19].

There are few population-based studies documenting the evaluation and progression of the conventional therapy-using patient of the UC disease phenotype. Thus, this study aims to describe the intestinal complications (IC) of patients with UC who started treatment with conventional therapies between January 2011 and January 2020 in the Brazilian healthcare system.

MATERIALS AND METHODS

Data source

For this study, data were collected from two Department of Informatics of the Brazilian Healthcare System (DATASUS) databases: Hospitalizations Information System (SIH), which contains hospitalization data[20] and the Outpatient Information System (SIA), which contains data on outpatient care [21,22].

The causes of hospital admissions are coded according to the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10). The SIH was used to identify the number and causes of hospital admissions related to UC and/or its IC.

The SIA is the system that allows local managers to process outpatient care information recorded in outpatient care capture applications by public and private providers contracted/agreed by the public healthcare system (SUS). Most SIA subsets have an ID code that enables linking the outpatient procedures to a single patient. Because SIH does not have patient ID information, a probabilistic record linkage (RLK) was performed allowing longitudinal assessment in SIH and SIA at a patient-level. The RLK relied on multiple steps with different combination of patient information from both databases, such as date of birth, gender and ZIP code, making it possible to identify patients in both systems.

Data is presented as procedure codes from billing records and includes demographic information, all procedures such as inpatient and outpatient performance, number of procedures, and other additional information.

Study design

The present study is a descriptive, observational, retrospective study of secondary data collected between 2011 and 2020, which used the DATASUS to characterize IC in patients with UC.

We considered UC patients those who had at least one report of UC ICD-10 code (K51). The date of the first request for UC conventional therapy was considered as the index date. Conventional therapies used for UC treatment were based on procedures codes available at DATASUS, according to the following list: Sulfasalazine; Mesalazine; Azathioprine; Methotrexate; Cyclosporine. UC patients must had at least two claims of conventional therapy to be included in the study. They were followed from the index date until the last information available in the DATASUS regardless of being under conventional treatment or not. One or more conventional therapies could had been used at the same time and/or in sequence by the patient, due to that line of treatment and comparisons between different conventional therapies were not assessed in this study.

We also assessed sociodemographic, such as age, sex and location of residency of the patient. Measurements of IC information in UC patients were extracted, including procedures performed, hospitalization causes, and diseases developing in the study sample. Each pre-defined claim of IC reported after conventional therapy initiation was considered as a progression of the UC disease.

Pre-defined claims of ICs were validated based on four independent medical expert opinions and literature about the natural history and evaluation of UC[23]. Patients who progressed from UC to malignant neoplasm of colon, stenosis, hemorrhage, ulcer or other specified diseases or symptoms of anus and rectum, functional diarrhea, megacolon, volvulus, intussusception or erythema nodosum or any intestinal surgery or hospitalization related to the disease was considered to have experienced an IC.

The following claims were considered as proxy of ICs: any claim for anus, rectum or intestinal surgeries for procedures, any claim of hospitalization reporting UC ICD-10 codes for hospitalization and/or any claim of ICD-10 code pre-defined for associated diseases [Table 1, list of diseases (ICD-10 code) considered as IC in consequence of underlying UC disease].

Overall ICs could reflect one or more type of ICs, so, in an attempt to represent them, IC analyses sets were stratified into 3 groups based on the type of IC: (1) Procedures: If claim of procedure code for anus, rectum or intestinal surgeries; (2) Hospitalizations: If claim of hospitalization for UC (reported UC ICD-10 in inpatient setting); and (3) Associated disease: If claim of ICD-10 code for diseases pre-defined as UC complications, such as C18 (malignant neoplasm of colon), K62.4 (stenosis of anus and rectum), K62.5 (hemorrhage of anus and rectum), K62.6 (ulcer of anus and rectum), K62.8 (other specified diseases of anus and rectum), K62.9 (disease of anus and rectum, unspecified), K59.1 (functional diarrhea), K59.3 (megacolon, not elsewhere classified), K56.2 (volvulus), K56.1 (intussusception), or L52 (erythema nodosum). Thus, to be considered a case of IC, patients must have at least one medical complaint in one or more of the sub-groups of ICs previously described.

In the data analysis, the annual IC in UC patients per each calendar year, and the incidence per 100 people of ICs were evaluated throughout the study. Patients whose UC progressed after the conventional treatment initiation timeframe were recorded as an IC annual rate and expressed year (from 1 to 5 years) according to the number of claims (total and mean) and the number of patients (total and percentage according to the number of patients in follow-up at the database at the respective year. Also, the mean ICs per each patient were assessed and expressed by calendar year. The incidence of IC was converted into units per patient/year by dividing them for all patients by the person-years of follow-up, because each individual attends a different time in the database. Thus, the incidence rate was calculated as the number of intestinal events divided by the total person-time at risk. Considering that one patient could present one or more types of IC, we also expressed the total of ICs found in the study.

The most frequent ICs related to procedures in UC population were assessed according to the number of patients with at least one procedure for anus, rectum or intestinal surgeries during the study period. The most frequent ICs related to associated disease in UC population was assessed according to the number of patients with at least one ICD-10 code of pre-defined associated-disease.

Study population

Patients were included in the study if they were aged ≥ 18 years old, if they had evidence of UC [at least one ICD-10 claim of UC (K51.0, K51.2, K51.3, K51.4, K51.5, K51.8 or K51.9)] and if they had at least one claim of conventional treatment of UC. The UC conventional therapies (synthetic) considered in the present study were sulfasalazine, mesalazine, azathioprine, methotrexate and cyclosporine.

To capture the initial stage of treatment, patients must have had no claims for conventional and/or anti-TNF therapy prior to the index date. Thus, the period from January 2010 to December 2011 was considered only for the evaluation of the medical history of patients who had the index date in 2011.

Considering that fissure and fistula of anal and rectal regions (K60) and/or abscess of anal and rectal regions (K61) are considered an uncommon IC in UC patients, but common in other IBD, we excluded patients with at least one ICD-10 claim of these diseases after index date (first claim of UC conventional treatment code). Additionally, patients with less than 6 months of follow-up in the database and patients who were not exclusive to the SUS were excluded. Non-SUS exclusive was defined as patients who used the SUS only to obtain high-cost medications and who carried out the rest of the treatment and medical care through their private health plan[24]. Thus, they are patients who had claims related to medications only.

Statistical analysis

Although only descriptive analyses were performed, a statistical review of the study was performed by a statistician. Results were described as measures of central tendency (means, medians) and spread (variance, range) for continuous variables (*e.g.*, age); absolute number and percentage for categorical variables (*e.g.*, sex) and Kaplan Meier Curve for time to event data. Ninety-five percent confidence intervals (95%CI) were calculated according to the variable, normal distribution for continuous variable, normal approximation to binominal distribution for proportion and Poisson distribution for incidence rate, as applicable.

Table 1 Description of most common intestinal complications related to associated diseases (International Statistical Classification of Diseases and Related Health Problems) or procedures (codes), *n* (%)

ICs	Description of ICs	Patients (<i>n</i> = 1273)	%	Procedure-related complications	Patients (<i>n</i> = 1125)	%	
Associated disease (ICD-10-related complications)				0407020403	Abdominal rectosigmoidectomy	167	15
K62	Other diseases of the anus and rectum	1070	78	0407020390	Body removed - rectum or colon polyps	145	13
C18	Malignant neoplasms of the colon	255	19	0407020063	Partial colectomy	135	12
K59	Other functional intestinal disorders	66	5	0407020209	Enterectomy and/or resection	128	11
L52	Erythema nodosum	27	2	0407020101	Colostomy	105	9
K56	Paralytic ileus and intestinal obstruction without hernia	3	0.2	0407020128	Dilatation of the anus and/or rectum	91	8
K51	Ulcerative colitis	2	0.1	0407020098	Abdominal colporrhaphy	51	5
C63	Malignant neoplasms of other and unspecified male genital organs	1	0.1	0407020241	Enterostomy closure	50	4
				0407020187	Enteroanastomy	41	4

Enterotomy is surgical incision into the intestine. ICs: intestinal complications; ICD: International Classification of Diseases.

The age variable was calculated based on the difference between the date of birth and the first conventional therapy claim reported (index date). The age was described as continuous variable, including the mean, standard deviation, median and quartiles. For the sex and race variables, they were described as categorical variables, with absolute frequencies and percentage.

Time of follow-up was calculated based on the difference between date of first claim of conventional therapy (index date) and the last date of patient information available at database. Conventional treatment profile of UC patients was evaluated and expressed by the percentage of patient who had at least one claim of UC therapy. Patients could change, add or stopped some of the conventional therapies (sulfasalazine, mesalazine, azathioprine, methotrexate and cyclosporine) during the treatment approach, therefore, the patient may have used one or more conventional therapies during the study period. Conventional treatment initiation was expressed as the number of patients (absolute and percentage) per calendar year (2011-2020) according to the first claim of the conventional therapy in the database. Timing using conventional therapy was calculated based on the first and the last claim of the therapy presented by the patient regardless of gaps. Switch conventional therapy was considered when it had at least one claim of different conventional therapy than the previous one. The time between one conventional therapy to another conventional therapy was described as continuous variable, including the mean, standard deviation, median and quartiles of the mean.

The main outcomes were regarding ICs in patients who initiated on conventional treatment between 2011 and 2020 in the SUS. Since each individual attended different amount of time in the database, some ICs parameters were analyzed as the frequency per person-years of follow-up. For incidence rate, confidence interval was estimated by Poisson rate confidence interval. The number of claims and the number of patients with at least one claim were expressed to address the total number of claim [patient could present more than one IC (claim) for the respective group of IC] and the total number of patients with at least one IC (claim).

Missing values were reported as missing information and imputation methods were not used. When needed, patient was censored for IC analyses. For Kaplan-Meier curve the last information available of the patient or the end of the study period was considered as censored for patients who did not present IC. IC was not assessed according to the conventional treatment received and neither if patient discontinued or not discontinued the conventional therapy treatment. Data was analyzed using Python version 3.6.9.

RESULTS

In the present study, a total of 41229 patients with UC meeting the inclusion criteria were exposed to conventional medications between 2011 to 2020 in DATASUS. Most patients were female (65%) and

were reported as white (56%). The mean \pm SD age was 48 ± 15.42 years old, with a mean \pm SD follow-up of 3.65 ± 2.27 years. Most patients (56%) were in the Southeast region of Brazil, followed by South (21%), and Northeast (14%) (Table 2).

All patients with UC had received conventional therapy and the mean \pm SD time using each was 2.64 ± 2.29 years. Regarding the conventional treatment profile for patients with UC, mesalazine had the highest proportion (87%). Azathioprine was the second (16%) and sulfasalazine the third (15%) most frequent drugs among patients with UC. Methotrexate was reported only by 1% of the patients and cyclosporine by less than 1% (Table 2).

Table 3 shows the incidence rate of bowel complications in patients with UC exposed to conventional treatment. The overall IR was 2.55 (2.46-2.63) per 100 patients. The IR of associated diseases (ICD-10-related), procedures-related and UC hospitalizations were 0.93 (0.89-0.98), 0.76 (0.71-0.80) and 0.97 (0.92-1.02), respectively. Considering that one patient could present more than one IC, a total of 6711 bowel complications claims were reported over the study period in these patients (Table 3).

Regarding the annual IC (overall and segregated types) in patients with UC, during the study period (≤ 1 year and 5 years), the overall complications rates were 2.90% at one year and 2.36% at 5 years. Segregated by type, complications related to the associated diseases (ICD-10) were 1.18% and 0.88%; the procedure-related complications were 0.71% and 0.68%; and the complications related to hospitalizations due to colitis was 1.10% and 0.84%, respectively (Table 4). The mean number of events per patient was also similar over the years for both the overall and the segregated IC types in patients with UC (Table 4). A description of the time to event for overall and segregated IC type in the population with UC is shown in Figure 1. In the Kaplan-Meier analysis, the probability to present any type of ICs (overall) was approximately 20% by the end of the study period. The segregated IC types had a comparable probability to present an event (less than 10% for procedures, hospitalization and associated disease) by the end of the study period (Figure 2).

From the 1273 patients with IC due to disease associated to UC found in the study, the categories Other diseases of the anus and rectum (78%), Colon malignant neoplasm (19%), Other functional intestinal disorders (5%) were the most common ones (Table 1).

Additionally, for the 1125 patients with IC due to procedures performed in consequence of the UC progression, it was found that abdominal rectosigmoidectomy (15%), body removed-rectal or colon polyps (13%) and partial colectomy (12%) were the most common ones (Table 1).

The length of hospitalization stay was 6.62 ± 6.62 d and the number of procedures performed during a hospitalization was 0.32 ± 0.28 . The most common hospitalization procedure was the treatment of non-infectious enteritis and colitis (77%), followed by diagnosis and/or emergency care at a medical clinic (7%) and treatment of other intestinal diseases (4%) (Table 5).

DISCUSSION

The present study described some specific categories of ICs in patients with UC treated with conventional therapies available in the public health system in Brazil between January 2011 and January 2020. Women, who were reported as white and from the Southeast region were the patients with the highest proportions in this study. The mean time of use of conventional therapy was 2.64 years and mesalazine was the most conventional therapy used. The mean age of UC patients treated with conventional medication in SUS was 48.86 years. This finding is similar to another database study, which reported that the highest proportion of patients with UC was in the 45-54 age group[25].

UC is considered a global burden due to its high prevalence and incidence in developed countries. Lima Martins *et al*[26], in 2014, carried out a study in Brazil, presenting a UC incidence of 5.3/100000 inhabitants/year. In São Paulo, Brazil the incidence of UC was 8/100000 inhabitants per year in 2015 [27]. A study carried out in an underdeveloped region of Northeastern in Brazil found an incidence of UC of approximately 0.6/100000 inhabitants per year in 2012[28].

Demographic characteristics of patients with UC in DATASUS showed that the large proportion of patients were from the Southeast region and the minority from the North region of Brazil. Although these regions represent one of the highest and lowest densities in the country, respectively, the number of UC cases in each region may also be due to social differences and inequalities in access to health services found in the country, in line with previous Brazilian perspectives findings reported in the literature[29].

Several studies have shown that uncontrolled UC is associated with structural damage and impaired gastrointestinal functioning[30]. This population-based study in Brazil depicted the year-by-year proportion of patients with IC under conventional therapy in SUS. During the first year and the last 5 years of follow-up, about 2.90% and 2.36%, respectively, of the patients had one or more IC in consequence of the UC progression. The rate of IC also appeared not to be high, similarly found in another international study. Thus, the proportion of patients with some complication seems to be constant over time even under treatment. It is known that continuing conventional therapy in some cases may delay more effective therapy and place patients at risk for worsening disease and complications[31].

Table 2 Demographic characteristics and follow-up of patients with ulcerative colitis treated with conventional therapies, n (%)

Variable	n	%
Patients	41229	100
Age ¹ , yr		
mean ± SD	48.86 ± 15.42	
Median (IQI)	48.09 (60.15-36.94)	
Sex		
Male	14417	35
Female	26812	65
Ethnicity		
White	23290	56
Black and other	11987	33
Missing	4643	11
CVT initiation		
2011	4300	10
2012	4054	10
2013	4259	10
2014	4877	12
2015	4846	12
2016	5039	12
2017	5565	13
2018	5040	12
2019	3249	8
Follow-up time ² , yr		
mean ± SD	3.65 (2.27)	
Median (IQI)	3.25 (1.75-5.26)	
Region of residence		
Southeast	22942	56
South	8831	21
Midwest	2638	6
Northeast	5833	14
North	985	2
Missing	0	0
Patients under CVT		
Mesalazine	35923	87
Sulfasalazine	6148	15
Azathioprine	6413	16
Ciclosporine	116	0
Methotrexate	290	1
Time using CVT ³ , yr		
mean ± SD	2.64 (2.29)	
Median (IQI)	1.92 (0.75-4.00)	
Patients switched treatment after first	2564	6

IC ⁴	
Time to switch treatment after IC, yr	
mean ± SD	0.36 (0.76)
Median (IQI)	0.08 (0.08-0.25)
Min	0.08

Values are expressed as numbers (%) or medians (range).

¹Age at index date.

²Time since index date up to the last date of patient information available in the database.

³Calculated based on the index date and the last claim of conventional therapy.

⁴Switching from one conventional therapy to another conventional therapy.

CVT: Conventional therapy; IQI: Interquartile interval; UC: Ulcerative colitis.

Table 3 Incidence of intestinal complications (overall and segregated types) in patients with ulcerative colitis considering all population at risk

	Total of events	First event ¹ (n)	PY ²	IR (95%CI)
Overall	6711	3616	141997.40	2.546 (2.464-2.628)
Associated disease (ICD-10-related)	3766	1372	146806.44	0.934 (0.885-0.983)
Procedure-related	1324	1125	148326.75	0.758 (0.714-0.802)
Colitis-related Hospitalization	1791	1426	147412.62	0.967 (0.917-1.017)

Incidence rate = n of patients with event/patient year \times 100.

¹Counted only the first intestinal complication (claim), but the patient could present with more than one IC (represented by the sum of the first claim).

²Patient year = sum of time of all patients under risk, since index date up to first IC or last available data.

ICs: Intestinal complications; IR: Incidence rate; ICD: International Classification of Diseases; PY: Patient year; UC: Ulcerative colitis.

Although the rates of ICs in the present study might be underestimated due to intrinsic limitation of the method applied, the impact of the progression of UC disease with consequent complication for the health system and patient might be significant, especially due to the severity and type of the complication generated for the patient. We found that almost 4% of the UC patients performed a surgery and/or procedure of anus or rectum during the study period. Surgical complications represent a substantial burden in terms of cost and quality of life, with reoperations, medical fees and additional hospital admissions being the main cost factors[13].

The associated diseases observed in the present study were mainly represented by other diseases of rectum and anus (78%) followed by the malignant neoplasm of colon (19%). Literature shows that UC patients with severe and persistent inflammation have an increased risk of developing neoplasm of colon[32]. In the United States, the prevalence of neoplasm of colon in a patient with UC was about 3.7% [33], in Spain was 11.7% [34]. It is well known that cancer is more likely to develop in patients with extensive colitis lasting 8-10 years or more[35]. In our investigation, the average follow-up period was only 3.65 years. Thus, it is possible that our results would be improved by a longer follow-up period.

Although no direct statistical comparison was performed, the incidence rates of ICs found in the present study indicate that ICs related to diseases associated to UC (ICD-10 code) were the highest, followed by those related to the procedure and finally hospitalization for UC. Only hospitalization related to ICD-10 of UC was considered in this study, which may imply underestimated rates. That is, if the patient was hospitalized due to the progression of the disease, other ICDs-10 codes were probably used and, therefore, was not counted in this study. Even though, we might assume that conventional therapy was not able to control the inflammatory process for all patients leading them to seek urgent and emergency services, or even been hospitalized and/or require surgeries procedures.

Conventional medical treatment for UC may have limited efficacy or serious adverse reactions[36]. Currently, 20% to 40% of patients with UC do not respond to conventional therapies and may receive secondary drug treatment or even colectomy. Anti-TNF agents were the first biologics to be used in the treatment of IBD, including infliximab and adalimumab. Other biologics therapies that target specific immune pathways has been implemented in several countries, including in Brazil, as potential therapeutics for UC[37,38]. In this line, Vedolizumab was recently approved by ANVISA for the treatment of adult patients with moderate to severe UC[39] who are not responding to one or more conventional treatments, such as steroids, immunosuppressive agents or TNF blockers[36]. However, during the study period, there was no biological therapy available in the SUS.

Table 4 Annual incidence of intestinal complications (overall and segregated type) in patients with ulcerative colitis over the study period (January 2011-February 2020)

	Overall		Associated disease (ICD-10-related)				Procedure-related				UC-related hospitalization					
	Patients (n)	%	Claims (n)	mean ± SD	Patients (n)	%	Claims (n)	mean ± SD	Patients (n)	%	Claims (n)	mean ± SD	Patients (n)	%	Claims (n)	mean ± SD
≤ 1 yr (n = 41229)	1197	2.90	1582	1.32 ± 1.3	487	1.18	763	1.57 ± 1.92	293	0.71	312	1.06 ± 0.29	456	1.10	520	1.14 ± 0.44
2 yr (n = 36389)	931	2.56	1250	1.34 ± 1.35	355	0.98	601	1.69 ± 2.08	262	0.72	284	1.08 ± 0.36	343	0.94	376	1.1 ± 0.32
3 yr (n = 28795)	716	2.49	953	1.33 ± 1.39	305	1.06	493	1.62 ± 2.05	182	0.63	201	1.1 ± 0.34	242	0.84	263	1.09 ± 0.34
4 yr (n = 22012)	531	2.41	668	1.26 ± 1.16	219	0.99	323	1.47 ± 1.72	158	0.72	170	1.08 ± 0.37	163	0.74	177	1.09 ± 0.32
5 yr (n = 16510)	389	2.36	457	1.17 ± 0.88	146	0.88	190	1.3 ± 1.36	113	0.68	115	1.02 ± 0.13	139	0.84	155	1.12 ± 0.36

n of patients: Counted only the number of patients with intestinal complications (ICs) (first IC), but patients could present with more than one IC. *n* of claims: Counted the total number of claims. ICs: Intestinal complications; ICD: International Classification of Diseases; IR: Incidence rate; UC: Ulcerative colitis.

The treatments available in the SUS until 2020 involved the use of aminosaliclates (sulfasalazine and mesalazine), corticosteroids (hydrocortisone and prednisone), immunosuppressants (azathioprine, 6-mercaptopurine and (intravenous cyclosporine), and antibiotics[40]. Biological therapy was included in the national protocol of UC treatment in early 2020[40,41]. Before that period, patients who needed biological therapy had to find other strategies besides the SUS to get biologic therapies for UC treatment, such as out of pocket, private healthcare and/or even judicial action.

Limitations

The main limitations of this study are related to the retrospective design of the study and the potential information biases and attrition of this study. With regard to information bias, the lack of information can lead to underestimation of results. Longitudinal and time-dependent analyzes of data correction are more accurate, however, DATASUS data end up being limited by this. Another limitation refers to the availability of medicines by the SUS, which are not always available and/or are available at different times during the period of this study, such as corticosteroids. Use of conventional therapy was an assumption based on the first claim of each drug at the database, so the patients could have not been under treatment during all the study period. However, as a real word study, this scenario reflects the daily life of UC patients. The severity of the disease was not considered in the analyses due to methodological limitations.

Additionally, for data analysis, the inpatient database (SIH) does not have patient identification and the use of probabilistic RLK, event rates may be underestimated, as they are mainly captured in outpatient databases (SIA). As it is a descriptive observational study, it is prone to confounding factors that are difficult to control or assess. In an attempt to reduce these biases, broad terms of procedures and ICD-10s related to possible complications were used. Although the ICD-10 codes used, procedures and hospitalization were predefined as ICs, other diseases and/or procedures related to UC could be codes could have been studied as ICs proxy, however, we were not able to predict all ICD-10.

Table 5 Length of hospitalization and most common procedures performed during hospitalization

Length of hospitalization and procedures	mean \pm SD	Median (IQR)	Procedures (inpatient most common procedures ¹)		Patients (n = 1426)	%
			ICs	Description of ICs		
Hospitalization (inpatient)			303070099	Treatment of enteritis and colitis not infectious	1103	77
Length of hospital stay, d (PPPY)	6.62 \pm 6.62	4.60 (2.63-8.11)	301060088	Diagnose and/or emergence care in medical clinic	102	7
Number of procedures performed (PPPY)	0.32 \pm 0.28	0.23 (0.15-0.38)	303070110	Treatment of other intestinal diseases	56	4
			301060070	Diagnosis and/or emergence care in surgery clinic	47	3
			415010012	Treatment with multiple surgeries	44	3
			415020034	Other procedures with following surgeries	30	2
			407020071	Total colectomy	29	2
			303070102	Treatment of digestive tract disease	23	2
			407020330	Total proctocolectomy	12	1
			303010061	Exploratory laparotomy	9	1

¹Inpatient procedures reported with ulcerative colitis disease International Statistical Classification of Diseases and Related Health Problems codes. ICs: Intestinal complications; ICD: International Classification of Diseases; IQR: Interquartile interval; PPPY: Per patient per year; UC: Ulcerative colitis.

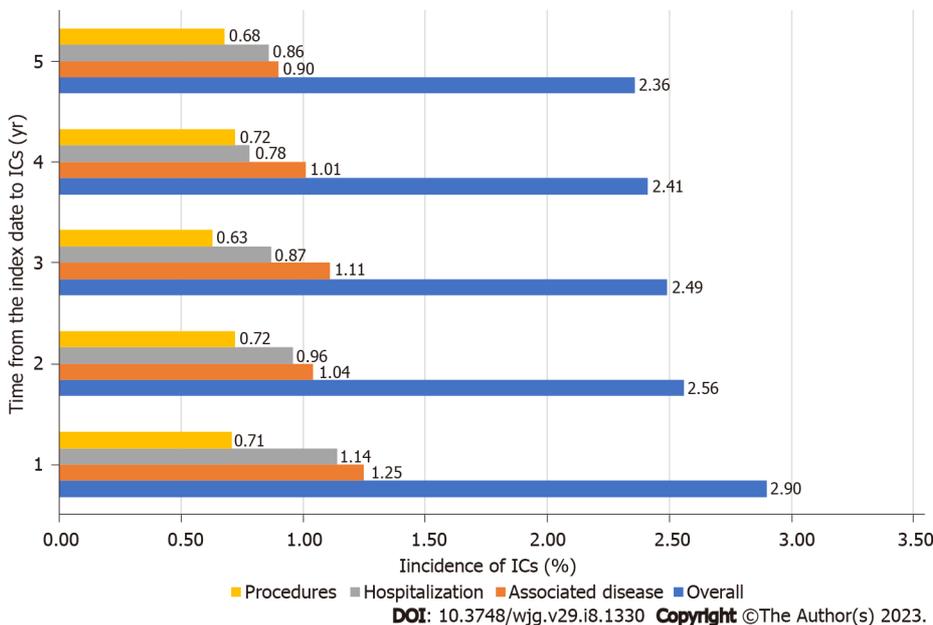


Figure 1 Annual intestinal complication (overall and segregated types) in ulcerative colitis patients over the study period (January 2011-February 2020). ICs: Intestinal complications.

CONCLUSION

UC have impact both for the population and public system (SUS) due to its clinical management and development of comorbidities and associated diseases. The results of this study highlight some issues regarding the progression of UC in patients who were treated with conventional therapies in the Brazilian public system showing that a percentage of UC patients have presented IC during the history of the disease. Most of the IC represent an important demand to the health system, with a need for health support and hospitalization. Current UC therapies, as well as innovative therapies that effectively alleviate UC symptoms, along with the implementation of an adequate program to access

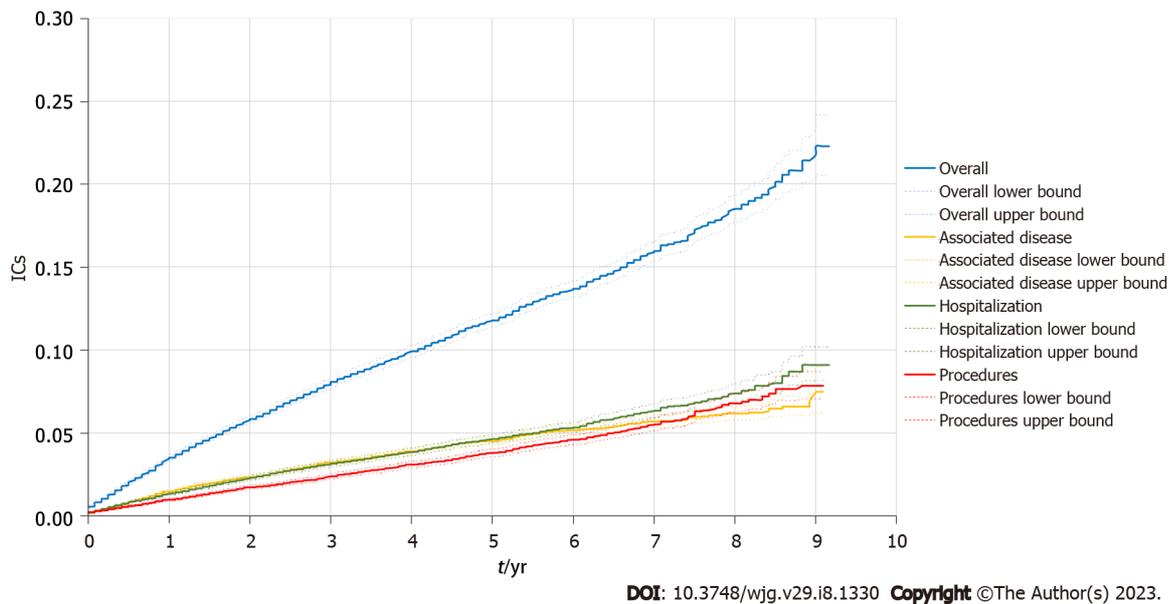


Figure 2 Kaplan-Meier curve depicting time to intestinal complication in ulcerative colitis patients. ICs: Intestinal complications.

and manage therapy for patients with UC, may improve the control or progression of UC and consequently decrease the negative the impact of the disease.

ARTICLE HIGHLIGHTS

Research background

This was an observational, descriptive, and retrospective study from 2011 to 2020 from the Department of Informatics of the Brazilian Healthcare System database.

Research motivation

To understand the real world situation of patients with ulcerative colitis (UC) in the public healthcare system.

Research objectives

Describe the intestinal complications (IC) of patients with UC who started conventional therapies.

Research methods

Patients ≥ 18 years of age who had at least one claim related to UC International Statistical Classification of Diseases and Related Health Problems (ICD-10) code and at least 2 claims for conventional therapies were included. IC was defined as at least one claim of: UC-related hospitalization, procedures code for rectum or intestinal surgeries, and/or associated disease defined by ICD-10 codes.

Research results

In total, 41229 UC patients were included. Overall IR of IC was 3.2 cases per 100 PY. Among the IC claims, 54% were related to associated diseases, 20% to procedures and 26% to hospitalizations. The overall annual incidence of IC was 2.9%, 2.6% and 2.5% in the first, second and third year after the first claim for therapy (index date), respectively. Over the first 3 years, the annual IR of UC-related hospitalizations ranged from 0.8% to 1.1%; associated diseases from 0.9% to 1.2%.

Research conclusions

Study shows that UC patients under conventional therapy seem to present progression of disease developing some IC, which may have a negative impact on patients and the burden on the health system.

Research perspectives

Biologics were implemented in the public healthcare system after the study period, it would be interesting to verify the IC impact of this implementation in patients with UC.

FOOTNOTES

Author contributions: Martins AL, Galhardi Gasparini R, Sasaki LY, Saad-Hossne R, Barreto TB, Marcolino T and Yang Santos C participated in designed, interpretation of the data and revised the article critically for important intellectual content; Ritter AMV participated in the acquisition, analysis and draft the initial manuscript.

Institutional review board statement: In alignment with Brazilian ethical resolution number 510, 2016, ethical approval was not necessary since this is a secondary study using anonymized data.

Conflict-of-interest statement: Martins AL served on the advisory board of Takeda, AbbVie, Janssen, Pfizer and Amgen and is a speaker for Amgen and Janssen. Galhardi Gasparini R is a speaker for Janssen, Takeda and AbbVie. Sasaki LY is a speaker for Janssen and Takeda and participated in the advisory boards of Takeda and AbbVie. Saad-Hossne R is a speaker and on the advisory boards for AbbVie, Takeda, Janssen, Pfizer, Fresenius and Amgen, as well as a speaker for Novartis. AMVR is an employee of IQVIA Brazil. Marcolino T, Barreto TB and Yang Santos C are employees of Takeda Pharmaceutical Brazil.

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