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Rehospitalization rates, costs, and risk factors for inflammatory bowel disease: a 16-year nationwide study

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Abstract

Aims: We aimed to describe the burden of rehospitalization in patients with inflammatory bowel disease (IBD), by evaluating rehospitalization rates, charges, and risk factors over 16 years.

Methods: We performed a retrospective analysis of all hospital discharges with a primary diagnosis of IBD in public hospitals between 2000 and 2015 in mainland Portugal from the Central Administration of the Health System (ACSS)'s national registry. We collected data on patient, clinical, and healthcare charges. We used survival analysis to estimate the rate and risk factors of IBD-related rehospitalization.

Results: We found that 33% ($n = 15{,}931$) of the IBD-related hospitalizations corresponded to rehospitalizations, which increased by 12% over 16 years. However, IBD rehospitalization rate per 100,000 IBD patients decreased 2.5-fold between 2003 and 2015. Mean IBD-related rehospitalization charges were €14,589/hospitalization-year in 2000 and €17,548 / hospitalization-year in 2015, with total rehospitalization charges reaching €3.1 million/year by 2015. Overall, the 30-day rate of rehospitalization was 24% for Crohn's disease (CD) and 22.4% for ulcerative colitis (UC). Novel risk factors for rehospitalization include penetrating disease in CD patients {hazard ratio (HR) 1.34 [95% confidence interval (CI) 1.20–1.51], $p < 0.001$} and colostomy in UC patients [HR 2.84 (95% CI 1.06–7.58)].

Conclusion: IBD-related rehospitalization should be closely monitored, and efforts to reduce its risk factors should be made to improve the quality of care and, consequently, to reduce the burden of IBD.

Keywords: burden, Crohn's disease, hospitalization, inflammatory bowel diseases, patient discharge, Portugal, registries, risk factors, ulcerative colitis

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Introduction

Inflammatory bowel disease (IBD) is an immune-mediated disease of unknown etiology presenting two major forms: Crohn's disease (CD) and ulcerative colitis (UC). Given its chronic nature and unpredictable disease course, IBD is associated with a considerable economic burden,[1,2] due mainly to productivity losses and healthcare costs (i.e. biologic therapy, hospitalizations).[3] Today, it is estimated that approximately 0.2–0.3% of the Portuguese population live with IBD. In 2030, this number is predicted to reach 0.3–0.5%.[4] Consequently, healthcare systems and society are progressively burdened by the increasing prevalence of IBD.[5,6]

The burden of chronic diseases on patients and healthcare systems may be reduced by assessing

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and improving the quality of healthcare, for example, by analyzing potential sources of costly but preventable clinical outcomes such as rehospitalizations.[7] Several studies have reported rehospitalization rates between 7% and 26%, and have identified rehospitalization risk factors in patients with IBD, mostly at 30 days after discharge.[8–14] In a recent systematic review with meta-analysis, Nguyen and colleagues[15] identified IBD flare, infection, or complications from unplanned surgeries as risk factors for IBD-related rehospitalizations at 30 days. On the other hand, decreases in IBD-related rehospitalization were associated with receiving steroids, undergoing colorectal surgery during the index admission, treatment at an institution with high-volume IBD admission, discharge on biologic therapy, and increasing patient age.[8,9,16]

However, there remains a paucity of data describing rehospitalizations in Portuguese patients with IBD, despite its importance on the evaluation of disease burden and quality of healthcare. In our previous study,[2] we determined the national hospitalization rate of IBD patients between 2000 and 2015 by using an administrative database of all patients subject to hospital discharge. In this study, using the same database, we aimed to describe the burden of rehospitalization, by evaluating rehospitalization rates and healthcare charges, and to analyze risk factors of rehospitalization in patients with IBD in mainland Portugal.

Material and methods

Study design and data source

The present study is part of a retrospective analysis of all IBD patients admitted to mainland Portuguese public hospitals previously described in detail.[2] Data were retrieved and collected from the Central Administration of the Health System (ACSS)'s national registry, which contains administrative data that concerns all patients subject to hospital discharge from hospitals governed by the National Health Service (NHS) in Portugal. We included all hospital discharges of patients with all ages and a primary diagnosis of IBD identified by the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes of 555.x (for CD) and 556.x (for UC), between 1 January 2000 and 27 December 2015. Hospitalizations presenting double diagnosis (CD and UC) were excluded. The first hospital discharge with a primary diagnosis of IBD during this study period was considered the index hospital discharge. The unit of observation was the hospital discharge.

Data collection

For each hospital discharge, the following data were collected: year (of hospital discharge date), hospital name, hospital admission date, hospital discharge date, admission type, age (at the time of hospital discharge), gender, area of residence, primary and secondary diagnosis, IBD-related medical procedures, and healthcare charges. Data on disease location/extension, IBD-related surgery, extraintestinal manifestations, anemia, malnutrition, anxiety, weight loss, wound complications, and depression were identified by the ICD-9-CM codes listed in Supplemental Table S1. The collected data also included inpatient's severity of illness (SOI) and risk of mortality, based on the ACSS's terms of reference for the contracting of health services in the Portuguese national health service (NHS),[17] and ranked according to the 3M™ All Patient Refined-Diagnosis Related Group methodology (APR-DRG, version 21).

Each record within the ACSS national registry contains individual deidentified patient identifiers, such as age, gender, and residence, that enabled researchers to create a unique patient ID, and to attribute multiple hospital discharges to the same individual. Hospital discharge will be referred as hospitalization hereafter.

Variables

Length of stay (LOS) was defined as the number of days between the hospital admission date and the discharge date for each hospitalization record. Hospital IBD discharge volume was defined as the number of IBD-related hospitalizations per year and categorized according to percentiles: low-moderate (⩽25 discharges/year), between the 50th and 75th percentiles; high–highest (26–139 discharges/year), between the 75th and 99th percentile. Fragmented care was defined as first subsequent hospitalization, attributed to the same individual, that did not occur in the same hospital of the index hospitalization (i.e., occurred in a different hospital).

Healthcare costs were estimated according to the Portuguese NHS reimbursements of hospital

healthcare charges, which are instituted by national legislation.[18] The cost analysis was derived from the 2009 expenditure tables because those were the latest to contemplate the 3M™ APR-DRG version 21, which spanned the entire study period.

Variables analyzed per patient: gender (female, male), disease extension (proctitis, proctosigmoiditis, left side, pancolitis), age (<20, 20–39, 40–59, ⩾60 years), LOS (1, 2–7, 8–14, >14 days), admission type (programmed, urgent), APR-DRG risk of severity (minor, moderate, major extreme), APR-DRG risk of mortality (minor, moderate, major extreme), IBD-related surgery (require operation, abdominal surgery, large intestinal resection, anal/rectal surgery, stoma surgery, colostomy, ileostomy, partial/total colectomy, total proctocolectomy), extraintestinal manifestations (pancreatic disease, mucocutaneous disease, musculoskeletal disease, hepatobiliary disease, blood/vascular disease, renal disease, ocular disease, bronchiectasis), hospital IBD discharge volume (low-moderate, high-highest), fragmented care (same hospital, different hospital), and other variables (anemia, smoking habits, wound complications, abdominal pain, malnutrition, weight loss, penetrating disease, bowel obstruction, perianal disease).

Variables analyzed per hospitalization: all aforementioned variables plus number of rehospitalizations per patient (1, 2–5, 6–10, >10), and time to rehospitalization (<30 days between first and second hospitalization, >30 days between first and second hospitalization).

Outcomes

The primary outcome measure was IBD-related rehospitalization, that is, at least one or more subsequent hospitalization(s) with a primary diagnosis of IBD attributed to the same individual occurring after the index hospitalization and during the study period. The time to rehospitalization was defined as the number of days between the hospitalization date of the index hospitalization and the hospital admission date of the first subsequent hospitalization. Rehospitalizations occurring ⩽30 days (i.e. short-term), 31–365 days (i.e. medium-term) or >365 days (i.e. long-term) from the index hospitalization date were analyzed.

Other outcome measures included the number of IBD-related rehospitalizations, rehospitalization rate per 100,000 inhabitants, rehospitalization rate per 100,000 hospitalizations, and rehospitalization rate per 100,000 IBD patients. The rehospitalization rate was calculated by dividing the number of rehospitalizations during the study period (numerator) by the total number of inhabitants, the total number of hospitalizations, or the total number of IBD patients (denominators) and multiplying by a factor of 100,000. The total number of inhabitants in mainland Portugal in the years analyzed, considered for computation of the rates, was obtained from the National Institute of Statistics (INE).[19] The prevalence of IBD in Portugal was estimated based on our previous publication,[4] where prevalence values were forecasted from 2008 to 2030.

Statistical analysis

Continuous variables were summarized by mean and standard deviation (SD), mean and minimum and maximum (min–max), or median and interquartile range (IQR), as applicable. Categorical variables were summarized by absolute (*n*) and relative (%) frequencies and compared using the chi-square test.

We analyzed trends in total rehospitalization rates per 100,000 inhabitants or hospitalizations or IBD patients over the study period. Total rehospitalization rates per 100,000 inhabitants or hospitalizations were analyzed by year and broken down by patient's characteristics (gender and age) and disease (IBD, CD, and UC). We estimated the mean (min-max) of the rehospitalization rates per 100,000 inhabitants or hospitalizations between 2000 and 2015.

We also analyzed trends in healthcare charges due to IBD-related rehospitalizations over time. The mean rehospitalization charges, in Euros, per hospitalization per year were estimated (€/hospitalization-year). Total rehospitalization charges were analyzed in million euros per year (M€/year) and broken down by disease (IBD, CD, and UC) and type of intervention (medical and surgical).

Due to the study design, no control group was established to assess risk factors for rehospitalization. Therefore, comparisons were performed between the groups "no rehospitalizations" and "rehospitalizations", the former being defined as a one-time hospitalization with absence of any subsequent hospitalization attributed to the same

individual, and the latter as multiple hospitalizations attributed to the same individual. Among the "rehospitalizations" group, the index hospitalization and the first subsequent rehospitalization were included in the analysis. The risk factors for rehospitalization at ⩽30 days and rehospitalization at 31–365 days, were also assessed.

To identify the risk factors associated with rehospitalization, a Cox regression model was used for univariate and multivariate analysis of the outcome of interest and other covariates. The period between the first and second hospitalizations was used as the time variable in the Cox regression.

Variables where a statistically significant difference ($p < 0.05$) was identified in the univariate analysis were included in the final multivariate regression modeling (backward method). The hazard ratio (HR) and 95% confidence intervals (CI) were estimated. The computed HR were adjusted for age, gender, LOS, risk of severity, risk of mortality, large intestine resection, anal/rectal surgery, ileostomy, partial/total colectomy, total proctocolectomy, anemia, wound complications, extraintestinal manifestations, penetrating disease, bowel obstruction, hospital volume, and fragmented care for the outcomes related with rehospitalizations.

The cumulative probabilities of being readmitted were calculated using the Kaplan–Meier method and compared between patients with CD and UC using the log-rank test.

Statistical significance was considered for $p < 0.05$. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) software (version 25.0), R statistical software (version 3.6.1), and RStudio (version 1.2.1335).

Results

Rehospitalizations

There was a total of 48,027 IBD-related hospitalizations in mainland Portugal public hospitals during the study period. We included in our study 33% of these total hospitalizations, corresponding to a total of 15,931 IBD-related rehospitalizations. Table 1 shows the demographic and clinical characteristics of the rehospitalizations by subtype of IBD; 77% concerned CD and 23% UC.

Globally, the number of rehospitalizations has increased by approximately 12%, from 780 in the year 2000 to 880 in the year 2015. Figure 1 provides an overview of the IBD-related rehospitalization rates. Rehospitalizations per 100,000 hospitalizations (Figure 1A) and per 100,000 inhabitants (Figure 1B) increased from 67.9 to 76.1 and from 7.5 to 8.5, respectively. Conversely, the rehospitalization rate per 100,000 IBD patients decreased 2.5-fold, from 6101 to 2421 between 2003 and 2015 (Figure 1C).

Crohn's disease. Over the 16-year study period, we found 12,242 rehospitalizations related to a primary diagnosis of CD from 8426 unique patients. The CD location was ileocolic in 3994 (33%) patients, ileal in 3520 (29%), and colic in 1392 (11%). Most of the CD-related rehospitalizations comprised young adults (20–39 years, 52%) and female patients (54%) (Table 1). Overall, the median LOS was 7 (3–12) days, and, in 17% of all rehospitalizations, the discharged patient required surgery (Table 1).

The IBD-related rehospitalization rates per 100,000 hospitalizations and 100,000 inhabitants are shown in Supplemental Table S2. Related to CD, the mean hospitalization rates were 64.1 (49.7–78.6) rehospitalizations per 100,000 hospitalizations and 7.3 (5.6–9.2) per 100,000 inhabitants. The absolute number of CD-related rehospitalizations increased from 571 in the year 2000 to 667 in the year 2015 (Supplemental Table S2). Accordingly, as shown in Figure 1, between 2000 and 2015, the CD-related hospitalization rate per 100,000 hospitalizations increased from 49.7 to 57.7 (Figure 1A) and per 100,000 inhabitants increased from 5.6 to 6.4 (Figure 1B). Similar increases were also observed when the rehospitalization rates per 100,000 inhabitants were analyzed by gender and age (Supplemental Table S2).

Ulcerative colitis. Over the 16-year study period, we found 3689 rehospitalizations related to a primary diagnosis of UC from 1114 patients (Table 1). The UC extension was found as pancolitis in 809 (22%) rehospitalizations, proctosigmoiditis in 356 (10%), left side in 232 (6.3%), and proctitis in 187 (5.1%). Most of the UC-related rehospitalizations comprised adults ⩾20 years-old (90%) and female patients (51%). The median LOS was 10 days (range 6–16) and surgery was required in 15% of all rehospitalizations.

Table 1. Characteristics of rehospitalizations by subtype of IBD (per hospitalization).

Characteristic	Primary diagnosis		*p* value[a]
	CD (*n* = 12,242)	UC (*n* = 3689)	
Age of patients, mean (SD), yr	36.8 (15.7)	45.1 (20.4)	<0.001
Age of patients group, *n* (%)			
<20 yr	1387 (11.3)	387 (10.5)	<0.001
20–39 yr	6307 (51.5)	1279 (34.7)	
40–59 yr	3347 (27.3)	980 (26.6)	
⩾60 yr	1201 (9.8)	1043 (28.3)	
Gender, *n* (%)			
Male	5675 (46.4)	1796 (48.7)	0.014
Female	6567 (53.6)	1893 (51.3)	
Admission type, *n* (%)			
Programmed	4083 (33.5)	1042 (28.3)	<0.001
Urgent	8123 (66.5)	2645 (71.7)	
No. of rehospitalizations per patient, *n* (%)			
1	3628 (29.6)	1496 (40.6)	<0.001
2–5	6619 (54.1)	1927 (52.2)	
6–10	1384 (11.3)	219 (5.9)	
>10	611 (5.0)	47 (1.3)	
Time to rehospitalization, *n* (%)			
<30 d between 1st and 2nd hospitalization	3166 (25.9)	910 (24.7)	0.150
>30 d between 1st and 2nd hospitalization	9076 (74.1)	2779 (75.3)	
LOS, median (IQR), days	7 (3–12)	10 (6–16)	<0.001
LOS, *n* (%)			
1 d	1774 (14.5)	221 (6.0)	<0.001
2–7 d	4873 (39.9)	1161 (31.6)	
8–14 d	3219 (26.4)	1181 (32.1)	
>14 d	2340 (19.2)	1116 (30.3)	
APR-DRG Severity of illness, *n* (%)			
Minor			0.011
Moderate	506 (13.1)	153 (12.3)	
Major	80 (2.1)	43 (3.5)	
Extreme	27 (0.7)	15 (1.2)	

(Continued)

Table 1. (Continued)

Characteristic	Primary diagnosis		*p* value[a]
	CD (*n* = 12,242)	UC (*n* = 3689)	
APR-DRG Risk of mortality, *n* (%)			
Minor	1772 (46.0)	424 (34.2)	<0.001
Moderate	1471 (38.1)	652 (52.6)	
Major	500 (13.0)	131 (10.6)	
Extreme	113 (2.9)	32 (2.6)	
IBD-related surgery, *n* (%)			
Require operation	48 (0.4)	8 (0.2)	0.157
Abdominal surgery	1040 (8.5)	149 (4.0)	<0.001
Large intestine resection	1480 (12.1)	258 (7.0)	<0.001
Anal/rectum surgery	208 (1.7)	397 (10.8)	<0.001
Stoma surgery	282 (2.3)	215 (5.8)	<0.001
Colostomy	113 (0.9)	10 (0.3)	0.029
Ileostomy	199 (1.6)	207 (5.6)	<0.001
Laparoscopic colectomy	103 (0.8)	0 (0.0)	<0.001
Colectomy (partial or total)	1376 (11.2)	216 (5.9)	<0.001
Total proctocolectomy	50 (0.4)	134 (3.6)	<0.001
Extraintestinal manifestations, *n* (%)			
Pancreatic disease	38 (0.3)	32 (0.9)	<0.001
Mucocutaneous disease	198 (1.6)	83 (2.2)	0.011
Musculoskeletal disease	224 (1.8)	87 (2.4)	0.047
Hepatobiliary disease	14 (0.1)	41 (1.1)	<0.001
Blood and vascular diseases	18 (0.1)	21 (0.6)	<0.001
Renal disease	20 (0.2)	7 (0.2)	0.655
Ocular disease	19 (0.2)	10 (0.3)	0.183
Bronchiectasis	14 (0.1)	8 (0.2)	0.202
Hospital IBD discharge volume, *n* (%)			
Low	446 (3.6)	197 (5.3)	<0.001
Moderate	2011 (12.6)	821 (22.3)	
High	4095 (33.5)	1100 (29.8)	

(Continued)

Table 1. (Continued)

Characteristic	Primary diagnosis		*p* value[a]
	CD (*n* = 12,242)	UC (*n* = 3689)	
Very high	4625 (37.8)	1306 (35.4)	
Highest	1065 (8.7)	265 (7.2)	
Other, *n* (%)			
Anemia	1417 (11.6)	887 (24.0)	<0.001
Malnutrition	182 (1.5)	57 (1.5)	0.822
Weight loss	216 (1.8)	75 (2.0)	0.293
Smoking habits	458 (3.7)	54 (1.5)	<0.001
Wound complications	233 (1.9)	55 (1.5)	0.107
Abdominal pain	905 (7.4)	165 (4.5)	<0.001
Penetrating disease	1449 (11.8)	57 (1.5)	<0.001
Bowel obstruction	1945 (15.9)	50 (1.4)	<0.001
Perianal disease	818 (6.7)	40 (1.1)	<0.001

APR-DRG, all patient refined-diagnosis related group; CD, Crohn's disease; d, days; IBD, inflammatory bowel disease; IQR, interquartile range; LOS, length of stay; SD, standard deviation; UC, ulcerative colitis; yr, years.
[a]*p*-values were calculated using the Chi-square test.

Related to UC, the mean hospitalization rates were 19.3 (15.2–24.2) rehospitalizations per 100,000 hospitalizations and 2.2 (1.8–2.7) per 100,000 inhabitants (Supplemental Table S2).

There was a small increase in the absolute number of UC-related rehospitalizations from the years 2009 to 2013. Accordingly, as shown in Figure 1, between 2000 and 2015, the UC-related rehospitalization rates per 100,000 hospitalizations or inhabitants increased from 18.2 to 18.4 (Figure 1A) and from 2.0 to 2.1 (Figure 1B), respectively. Similar increases were observed when the rehospitalization rates per 100,000 inhabitants were analyzed by gender and age (Supplemental Table S2).

Healthcare charges due to rehospitalization

Figure 2 displays the change of the annual charges on rehospitalizations of IBD patients throughout the 16-year study period. Concerning the mean rehospitalization charges of IBD, the values varied from €14,589/hospitalization-year in 2000 to €17,548/hospitalization-year in 2015 (Figure 2A). Conversely, the total charges related to IBD-related rehospitalizations have increased from €2.1 M/year in 2000 to €3.1 M/year in 2015, due mainly to an increase in the total charges on CD-related rehospitalizations (Figure 2B).

Crohn's disease. The mean charges of CD-related rehospitalizations were €7844/hospitalization-year in 2000 and €8887/hospitalization-year in 2015 (Figure 2A). The average of the total rehospitalization charges was estimated to be €2.6 M/year (2000–2015: €1.6–2.5 M/year, Figure 2B).

The average of mean rehospitalization charges related to surgical interventions in CD patients was approximately two-times higher than the average of those related to medical interventions: €5385/hospitalization-year (2000–2015: €4883–5766/hospitalization-year) and €2951/hospitalization-year (2000–2015: €2961–3121/hospitalization-year), respectively (see Supplemental Figure S1A). Notwithstanding, the average total annual charges related to medical interventions was higher than the average of those related to surgical interventions: €1.6 M/year (2000–2015: €1.1–1.6 M/year) and

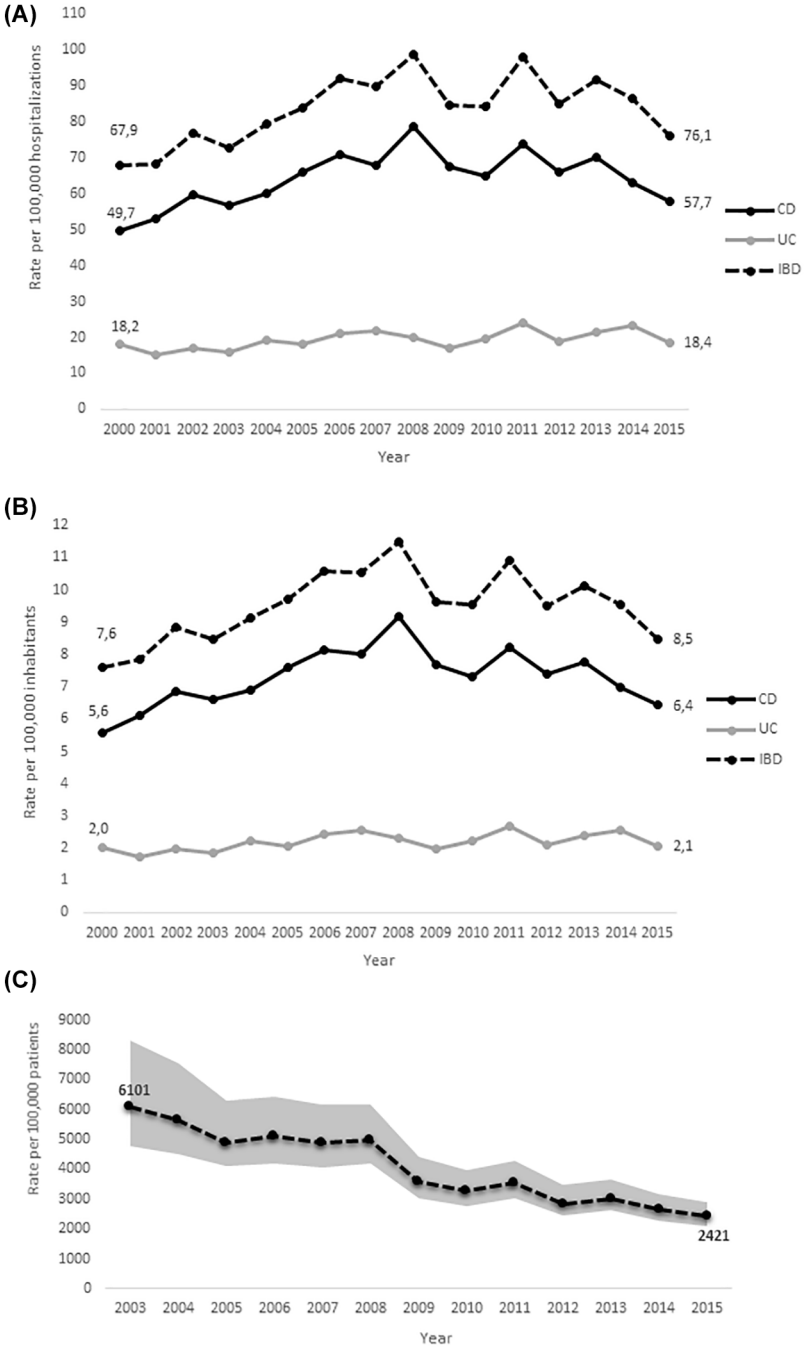

Figure 1. Rehospitalization rates of IBD, CD, and UC per (A) 100,000 hospitalizations, (B) 100,000 inhabitants, and (C) 100,000 IBD patients in mainland Portugal, 2000–2015
Shaded region in (C) represents standard deviation (SD).
CD, Crohn's disease; IBD, inflammatory bowel disease; UC, ulcerative colitis.

€1.0 M/year (2000–2015: €0.5–0.9 M/year), respectively (Supplemental Figure S1B).

Ulcerative colitis. The mean charges regarding rehospitalization of UC patients varied between €6745/hospitalization-year in 2000 and €8661/hospitalization-year in 2015. Total charges averaged €0.7 M/year (2000–2015: €0.5–0.7 M/year, Figure 2B).

Similar to CD, in UC the average of the mean rehospitalization charges related to surgical

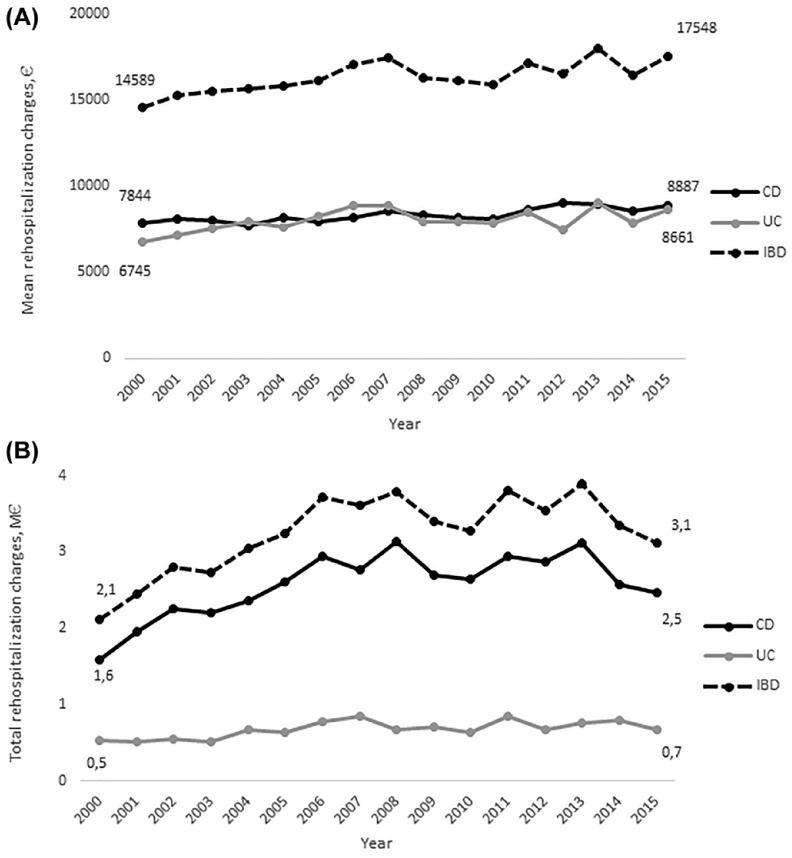

Figure 2. Change of annual (A) mean rehospitalization charges and (B) total rehospitalization charges of IBD, CD, and UC patients in mainland Portugal, 2000–2015.
CD, Crohn's disease; IBD, inflammatory bowel disease; M, million; UC, ulcerative colitis.

interventions was approximately 2-fold higher than the average of those related to medical interventions: €5193/hospitalization-year (2000–2015: €3908–5832/hospitalization-year) and €2833/hospitalization-year (2000–2015: €2838–2829/hospitalization-year), respectively (see Supplemental Figure S2A). Still, the average of the total annual charges related to medical interventions was higher than the average of those related to surgical interventions: €0.5 M/year (2000–2015: €0.4–0.5 M/year) and €0.1 M/year (2000–2015: €0.2–0.2 M/year), respectively (Supplemental Figure S2B).

Risk factors associated with rehospitalization

In time-to-event analysis, UC was associated with a lower risk of rehospitalization [HR = 0.91 (0.85–0.96), $p = 0.002$] (Figure 3). The cumulative rehospitalization rates were higher for CD than UC, with 30-day rehospitalization rates of 24.0% *versus* 22.5% (log-rank test, $p = 0.002$). After

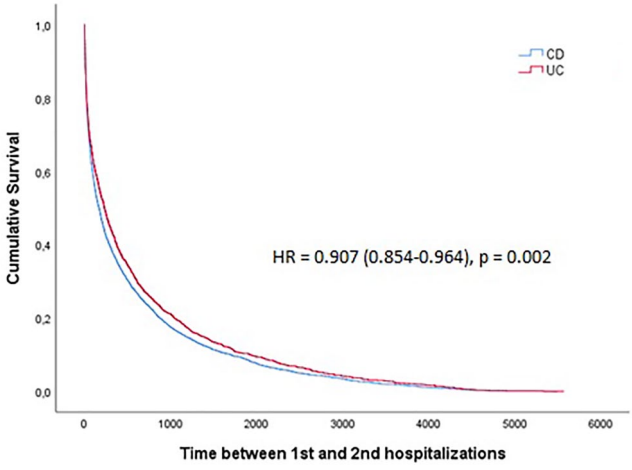

Figure 3. Kaplan–Meier survival curves for rehospitalization after index hospitalization stratified by IBD type. The survival curves were significantly different (log-rank test, $p = 0.002$).
CD, Crohn's disease; HR, hazard ratio; IBD, Inflammatory bowel disease; UC, ulcerative colitis.

Table 2. Multivariate analysis of risk factors associated with rehospitalization of CD patients (time between first and second hospitalization).

Characteristic	*n* (%)		Adjusted HR (95% CI)	*p* value
	No rehospitalization[a] (*n* = 4797)	Rehospitalization[b] (*n* = 3628)		
Disease extension[c]				
Ileal	1778 (37.1)	1153 (31.8)	**1.141 (1.063-1.225)**	**<0.001**
Age of patients group				
⩾60 yr	814 (17.0)	369 (10.2)	1 [Reference]	
<20 yr	648 (13.5)	516 (14.2)	**1.187 (1.037–1.358)**	**0.013**
20–39 yr	2229 (46.5)	1852 (51.0)	1.114 (0.995–1.247)	0.060
40–59 yr	1107 (23.1)	891 (24.6)	1.041 (0.921–1.176)	0.522
IBD-related surgery[c]				
Abdominal surgery	379 (7.9)	217 (6.0)	0.872 (0.744–1.022)	0.090
Large intestinal resection	542 (11.3)	313 (8.6)	**0.616 (0.536–0.707)**	**<0.001**
Ileostomy	22 (0.5)	59 (1.6)	**1.565 (1.174–2.087)**	**0.002**
Total proctocolectomy	11 (0.2)	6 (0.2)	**0.292 (0.130–0.655)**	**0.003**
Other[c]				
Wound complications	63 (1.3)	51 (1.4)	1.341 (0.993–1.810)	0.056
Penetrating disease	304 (6.3)	370 (10.2)	**1.345 (1.199–1.509)**	**<0.001**
Perianal disease	117 (2.4)	182 (5.0)	**1.259 (1.082–1.464)**	**0.003**

Significant HR in boldface.
CD, Crohn's disease; CI, confidence interval; d, days; IBD, inflammatory bowel disease; LOS, length of stay; HR, hazard ratio; yr, years.
[a]Refers to one-time hospital discharge with absence of any subsequent hospitalization attributed to the same individual.
[b]Refers to multiple hospital discharges attributed to the same individual.
[c]For each HR, analyzed as dichotomous variables with two categories: presence *versus* absence (absence as a reference category).

365 days of discharge, rehospitalization rates of CD and UC were, respectively, 40.0% and 35.4% (log-rank test, $p = 0.002$).

Crohn's disease. Regarding CD, univariate analysis revealed crude HR for rehospitalization (data not shown, see Supplemental Table S3). In the multivariate regression, factors significantly associated with increased risk of rehospitalization included: younger age (<20 years old), ileostomy, penetrating disease, and perianal disease (Table 2).

On the other hand, large intestinal resection, and total proctocolectomy were significantly associated with decreased risk of rehospitalization (Table 2).

Ulcerative colitis. Regarding UC, the results of the univariate analysis are summarized in Supplemental Table S4. In the multivariate regression, factors significantly associated with increased risk of rehospitalization included large intestinal resection, colostomy, smoking habits, malnutrition, and weight loss (Table 3).

On the other hand, we found no significant factors significantly associated with decreased risk of rehospitalization (Table 3).

Table 3. Multivariate analysis of risk factors associated with rehospitalization of UC patients (time between first and second hospitalization).

Characteristic	*n* (%)		Adjusted HR[c] (95% CI)	*p* value
	No rehospitalization[a] (*n* = 2869)	Rehospitalization[b] (*n* = 1496)		
IBD-related surgery[c]				
Large intestinal resection	102 (3.6)	74 (4.9)	**1.396 (1.103–1.767)**	**0.005**
Colostomy	22 (0.8)	4 (0.3)	**2.836 (1.060–7.582)**	**0.038**
Other[c]				
Anemia	604 (21.0)	354 (23.7)	1.125 (0.997–1.268)	0.056
Smoking habits	60 (2.1)	18 (1.2)	**2.113 (1.323–3.377)**	**0.002**
Malnutrition	31 (1.1)	18 (1.2)	**1.730 (1.085–2.759)**	**0.021**
Weight Loss	41 (1.4)	44 (2.9)	**1.449 (1.069–1.965)**	**0.017**

Significant HR in boldface.
CI, confidence interval; d, days; HR, hazard ratio; IBD, inflammatory bowel disease; LOS, length of stay; UC, ulcerative colitis; yr, years.
[a]Refers to one-time hospital discharge with absence of any subsequent hospitalization attributed to the same individual.
[b]Refers to multiple hospital discharges attributed to the same individual.
[c]For each HR, analyzed as dichotomous variables with two categories: presence *versus* absence (absence as a reference category).

Risk factors associated with rehospitalization ⩽30 days

Crohn's disease. Univariate analysis of HR for rehospitalization ⩽30 days are shown in Supplemental Table S5. In the multivariate regression, factors associated with increased risk of rehospitalization ⩽30 days included: age <20 years and 20–39 years, and penetrating disease (Table 4).

On the other hand, colic disease was associated with decreased risk of rehospitalization ⩽30 days (Table 4).

Ulcerative colitis. Univariate analysis is shown in Supplemental Table S6. In the multivariate regression, factors associated with increased risk of rehospitalization ⩽30 days were male gender and wound complications. However, a higher hospital IBD discharge volume was associated with decreased risk of rehospitalization ⩽30 days, compared with a lower volume (Table 5).

Risk factors associated with rehospitalization 31–365 days

Crohn's disease. Univariate analysis for rehospitalization 31–365 days are shown in Supplemental Table S7. On multivariable analysis, factors associated with increased risk of rehospitalization 31–365 days included: ileal disease, stoma surgery, smoking habits, penetrating disease, and perianal disease (Table 6).

On the other hand, abdominal surgery and partial/total colectomy were associated with decreased risk of rehospitalization 31–365 days (Table 6).

Ulcerative colitis. Univariate analysis is shown in Supplemental Table S8. In the multivariate regression, factors associated with increased risk of rehospitalization 31–365 days included: large intestinal resection, hepatobiliary disease, anemia, and malnutrition (Table 7).

However, we found no significant factors significantly associated with decreased risk of rehospitalization 31–365 days (Table 7).

Discussion

This study set out to evaluate the rehospitalization rates, costs, and risk factors in IBD patients, based on a retrospective analysis of a nationwide database of all hospitalizations from public

Table 4. Multivariate analysis showing risk factors associated with rehospitalization ⩽30 days of CD patients (time between first and second hospitalization).

Characteristic	*n* (%)		Adjusted HR[a] (95% CI)	*p* value
	Rehospitalization >30 days (*n* = 2752)	Rehospitalization ⩽30 days (*n* = 876)		
Disease extension[a]				
Colic	352 (12.8)	85 (9.7)	**0.779 (0.622–0.974)**	**0.029**
Age of patients group				
⩾60 yr	301 (10.9)	68 (27.8)	1 [Reference]	
<20 yr	357(13.0)	159 (18.2)	**1.859 (1.397–2.475)**	**<0.001**
20–39 yr	1391 (50.5)	461 (52.6)	**1.376 (1.064–1.780)**	**0.015**
40–59 yr	703 (25.5)	188 (21.5)	1.168 (0.884–1.543)	0.276
Other[a]				
Penetrating disease	256 (9.3)	114 (13.0)	**1.418 (1.164–1.728)**	**0.001**

Significant HR in boldface.
CD, Crohn's disease; CI, confidence interval; IBD, inflammatory bowel disease; OR, odds ratio; yr, years.
This analysis compares patients who have been readmitted in less than 30 days to those who have been readmitted in more than 30 days.
[a]For each HR, analyzed as dichotomous variables with two categories: presence *versus* absence (absence as a reference category).

Table 5. Multivariate analysis of risk factors associated with rehospitalization ⩽30 days of UC patients (time between first and second hospitalization).

	n (%)		Adjusted HR[a] (95% CI)	*p* value
	Rehospitalization >30 days (*n* = 1153)	Rehospitalization ⩽30 days (*n* = 343)		
Gender				
Female	602 (52.2)	157 (45.8)	1 (Reference)	
Male	551 (47.8)	186 (54.2)	**1.261 (1.017–1.564)**	**0.035**
Hospital IBD discharge volume				
Low–moderate	345 (29.9)	121 (35.3)	1 (Reference)	
High–highest	808 (70.1)	222 (64.7)	**0.774 (0.618–0.970)**	**0.026**
Other[a]				
Wound complications	5 (0.4)	5 (1.5)	**2.918 (1.201–7.089)**	**0.018**

Significant HR in boldface.
CI, confidence interval; d, days; HR, hazard ratio; IBD, inflammatory bowel disease; LOS, length of stay; UC, ulcerative colitis; yr, years.
This analysis compares patients who have been readmitted in less than 30 days to those who have been readmitted in more than 30 days.
[a]For each HR, analyzed as dichotomous variables with two categories: presence *versus* absence (absence as a reference category).

Table 6. Multivariate analysis of risk factors associated with rehospitalization between 31 and 365 days after index hospitalization of CD patients (time between first and second hospitalization).

Characteristic	*n* (%)		Adjusted HR[a] (95% CI)	*p* value
	Rehospitalization 31–365 days (*n* = 1450)	Rehospitalization >365 days (*n* = 1302)		
Disease extension[a]				
Ileal	481 (33.2)	380 (29.2)	**1.176 (1.052–1.314)**	**0.004**
IBD-related surgery[a]				
Abdominal surgery	63 (4.3)	113 (8.7)	**0.642 (0.488–0.845)**	**0.002**
Stoma surgery	49 (3.4)	15 (1.2)	**2.258 (1.632–3.124)**	**<0.001**
Partial/total colectomy	83 (5.7)	157 (12.1)	**0.489 (0.380–0.629)**	**<0.001**
Other[a]				
Smoking habits	70 (4.8)	37 (2.8)	**1.317 (1.034–1.678)**	**0.026**
Penetrating disease	151 (10.4)	105 (8.1)	**1.361 (1.133–1.634)**	**0.001**
Perianal disease	86 (5.9)	48 (3.7)	**1.391 (1.117–1.733)**	**0.003**

Significant HR in boldface.
CD, Crohn's disease; CI, confidence interval; IBD, inflammatory bowel disease; OR, odds ratio; yr, years.
This analysis compares patients who have been readmitted between 31 and 365 days to those who have been readmitted in more than 365 days.
[a]For each HR, analyzed as dichotomous variables with two categories: presence *versus* absence (absence as a reference category).

hospitals in mainland Portugal. Identifying risk factors of IBD-related rehospitalization will allow future revisions and improvements of healthcare systems, and, ultimately, reduce the burden associated with rehospitalization.

We found that 33% of hospitalizations with a primary diagnosis of IBD corresponded to rehospitalizations (CD: 77%; UC: 23%), which increased by 12% from 2000 to 2015. However, we observed a 2.5-fold decrease in the rehospitalization rate between 2003 and 2015 when adjusting for the forecasted population of IBD patients. This finding may be explained by the paradigm shift in the management of IBD introduced by the use of biologic therapy, such as infliximab, which reduces the risk of hospitalization and surgery.[20] However, a recent Canadian study revealed that infliximab did not yield the expected reduction in the hospitalization rate of Ontario IBD patients.[21] In our study, the analysis of the biologic therapy's role in the reduction of rehospitalization rates was limited by the absence of ICD-9-CM codes for this therapy.

Although cost profiles may be changing from surgery and hospitalizations towards biologic therapy,[3,22,23] several studies have shown that hospitalization is one of the main contributors to direct costs in IBD.[24–27] In Canada, direct healthcare costs of IBD were estimated to surpass the 1 billion Canadian dollar mark in 2018.[28] In Portugal, we found an increasing trend in the mean and total charges for CD- and UC-related rehospitalizations from 2000 to 2015 being accompanied by an increase in rehospitalizations in the same period. When compared with our previous study on hospitalizations,[2] we observed that the mean charges on IBD rehospitalizations are two-fold higher than IBD hospitalizations (€14,589–17,548/patient-year *versus* €6215–6722/patient-year in 2000–2015) with total IBD-related rehospitalization charges reaching €3.1 M/year by 2015.

The above-mentioned numbers are representative of the economic burden of rehospitalization in mainland Portugal and its potential for reducing healthcare costs. The significant economic burden of rehospitalization in IBD patients has been previously demonstrated by Hazratjee and

Table 7. Multivariate analysis of risk factors associated with rehospitalization between 31 and 365 days after index hospitalization of UC patients (time between first and second hospitalization).

	n (%)		Adjusted HR[a] (95% CI)	*p* value
	Rehospitalization 31 – 365 days (*n* = 556)	**Rehospitalization > 365 days (*n* = 603)**		
IBD-related surgery[a]				
Large intestinal resection	43 (7.7)	18 (3.0)	**1.885 (1.380–2.576)**	**<0.001**
Extraintestinal manifestations[a]				
Hepatobiliary disease	8 (1.4)	3 (0.5)	**2.319 (1.153–4.665)**	**0.018**
Other[a]				
Anemia	145 (26.1)	121 (20.1)	**1.298 (1.074–1.569)**	**0.007**
Malnutrition	11 (2.0)	3 (0.5)	**2.232 (1.226–4.062)**	**0.009**

Significant HR in boldface.
CI, confidence interval; d, days; HR, hazard ratio; IBD, inflammatory bowel disease; LOS, length of stay; UC, ulcerative colitis; yr, years.
This analysis compares patients who have been readmitted between 31 and 365 days to those who have been readmitted in more than 365 days.
[a]For each HR, analyzed as dichotomous variables with two categories: presence *versus* absence (absence as a reference category).

colleagues,[12] who reported that rehospitalizations within 30 days of the index hospitalization increased the cost of care by 111%. In another study, Barnes and colleagues observed that rehospitalizations within 90 days lead to $576 million in excess costs.[29]

We also aimed to identify the rehospitalization rate and risk factors for both CD and UC patients, through a time-to-event analysis.

Similarly to Nguyen and colleagues, we found that UC patients present a 9% lower risk of rehospitalization when compared with CD patients.[16] Moreover, the rehospitalization rate at the 30-day mark (CD: 24.0%; UC: 22.5%) was higher than previously reported in a systematic review with meta-analysis by the same group.[15] The difference in findings may be driven by CD-related hospitalization, which corresponds to approximately 75% of the overall number of hospitalizations in this study.

Besides age group, ileostomy and perianal disease, which were previously described in the literature,[9,10,30,31] presenting penetrating disease in the index hospitalization is also associated with rehospitalization in CD. A penetrating phenotype as a risk factor for rehospitalization is in accordance with Kruger and colleagues, who reported that CD patients with more severe disease on index admission presented higher rates of rehospitalization and mortality.[14]

Apart from large intestinal resection, smoking habits, malnutrition, and weight loss, which were already reported,[9,10,16] we identified colostomy as a novel risk factor for rehospitalization in UC patients. Patients undergoing ostomy creation present higher rates for rehospitalization, due mostly to dehydration and post-operative complications.[30,32,33]

Furthermore, we aimed to identify the risk factors for short- and medium-term IBD-related rehospitalization (⩽30 days and 31–365 days). As far as we know, our study appears to be the first report on such an analysis from a nationally representative cohort of rehospitalizations. In agreement with the aforementioned general analysis, we have found that a younger age group (<20 years and 20–39 years) and penetrating disease are risk factors for rehospitalization ⩽30 days in CD patients. Additionally, and in accordance with two administrative retrospective studies, we identified male gender and wound complications as risk factors for rehospitalization ⩽30 days in UC patients.[9,13]

Regarding medium-term rehospitalization (31–365 days), we identified several potentially modifiable risk factors among patients with CD and UC, including stoma surgery, smoking habits, large

intestinal resection, anemia, and malnutrition. These results are consistent with previous reports on early and late readmission.[9,16,30,31,34]

It is noteworthy that we also identified factors associated with a decreased risk for CD-related rehospitalization, such as colic disease and surgery (large intestinal resection, total proctocolectomy, colectomy, and abdominal surgery). We also found a protective association between high hospital IBD discharge volume and rehospitalization in UC patients, as demonstrated in a study by Nguyen and colleagues.[16,35] Therefore, focusing on the timely performance of surgical interventions, and having access to optimal monitoring and management of the disease, are promising strategies to decrease rehospitalizations.

The key strengths of this study are the utilization of an administrative database with national coverage, ensuring the representativeness of the data to a nationwide scale, and the novelty of this study in mainland Portugal. On the other hand, this study was limited by its retrospective and registry based design, which might have led to data misclassification by inaccurate coding and validation, as well as to eventual underreporting. As an example, disease extent is not mandatory, thus frequencies in the columns may not sum up to 100% due to missing data. Nevertheless, several studies have already validated the suitability of the ICD-9-CM coding system in the IBD context.[36,37] Additionally, treatment exposure was not assessed since ICD-9-CM does not allow the codification of biological treatment. Another limitation is that only public hospitals were included in this study, therefore private hospitalizations were not considered. Finally, we only used the 2009 expenditure tables with the 3M™ APR-DRG version 21, which may underappreciate any price fluctuations regarding IBD-related charges that occurred subsequently. Any DRG changes were also not considered.

Conclusion

To obtain an accurate portrayal of readmission in IBD, it is of great importance to adjust the number of rehospitalizations to the prevalence of the disease. As we have shown, IBD patients are becoming readmitted less over time.

We have also observed that mean rehospitalization charges are pricier than hospitalizations. This reveals a potential way to substantially diminish healthcare costs should readmissions be reduced.

Additionally, novel risk factors for rehospitalization were identified: penetrating disease in CD patients and colostomy in UC patients.

In conclusion, rehospitalization should be closely monitored, and efforts to reduce its risk factors should be made to improve the quality of care, and, consequently, to reduce the burden of IBD.

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Contributors

Study conception or design: CCD, FM; Data collection: CCD; Data analysis and interpretation: MS, CCD, FM; Drafting of the manuscript: MS; Critical revision of the manuscript: CCD, FM;

All authors approved the final version of the manuscript and take responsibility for the accuracy or integrity of any part of the work.

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Conflict of interest statement

FM has received speaker fees from: AbbVie, Ferring, Falk, Hospira, PharmaKern, MSD,

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Patient consent for publication

Not required due to the administrative retrospective nature of the study.

Ethical Approval

All study procedures were approved by the São João Hospital Center Ethics Committee on 14 September 2018, and conducted in accordance with the Declaration of Helsinki.

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Data Sharing

All data relevant to the study are included in the article or uploaded as supplemental information.

Supplemental material

Supplemental material for this article is available online.

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