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***Ten-year time evolution of Inflammatory Bowel Disease:  
Reality from a Tertiary Hospital***

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Reality from a Tertiary Hospital***

ORIGINAL ARTICLE

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## **ABBREVIATIONS**

Anti-TNF – Tumor necrosis factor antagonists

CD – Crohn's Disease

IBD – Inflammatory Bowel Disease

IQR – Inter-quartile range

UC – Ulcerative Colitis

SES-CD – Simple Endoscopic Score for Crohn's Disease

## **ABSTRACT**

**Introduction:** Epidemiology and therapeutic approach to inflammatory bowel disease (IBD) have shown substantial changes in recent years. This study aims to investigate the temporal evolution of IBD by evaluating its related hospitalizations and putative differences regarding patients' characteristics and potential associated prognostic factors.

**Methods:** Retrospective single-center cohort study. Evaluation of demographic, clinical, analytical and endoscopic data of adult IBD-patients, hospitalized in a Gastroenterology department of a tertiary hospital in 2010-2011 and 2020-2021. Admissions were due to active disease or in case of adverse events of IBD-related therapies. Potential prognostic factors assessed were: time disease-hospitalization, length of hospitalization, analytical parameters on admission, therapies prior to and during hospitalization and development of complications.

**Results:** Inclusion of 192 hospitalizations from 150 patients (58.7% male), of whom 60% had Crohn's disease (CD) and 40% Ulcerative Colitis (UC). Active disease was the indication for hospitalization in 187 (97.4%) cases and 5 (2.6%) were due to adverse events of therapies. CD patients were significantly younger at diagnosis ( $p=0.005$ ) and had more previous IBD-related surgeries ( $p=0.021$ ). Number of rehospitalizations decreased significantly from one study period to the other ( $p=0.025$ ) and the use of biological therapy had an opposite evolution ( $p<0.001$ ). The administration of blood transfusions during the first hospitalization was found as a potential prognostic factor associated with rehospitalizations ( $p=0.046$ ).

**Conclusion:** In a ten-year period of time, a decrease in IBD-related therapies' adverse events, a decrease in IBD-related rehospitalizations and an increase in the use of biological therapies were verified. The necessity of blood transfusions seems to be a risk factor for rehospitalization.

**Keywords:** Inflammatory Bowel Disease, Crohn's Disease, Ulcerative Colitis, Hospitalizations, Prognosis

## RESUMO

**Introdução:** A epidemiologia e a abordagem terapêutica da doença inflamatória intestinal (DII) têm sido alvo de uma evolução substancial. O presente estudo tem como objetivo investigar a evolução temporal da DII, através da avaliação dos seus internamentos, de possíveis diferenças nas características e potenciais fatores de prognóstico associados.

**Métodos:** Estudo de coorte retrospectivo em centro único. Avaliação de dados demográficos, clínicos, analíticos e endoscópicos de doentes internados por DII, no serviço de gastroenterologia de um hospital terciário, durante os períodos de 2010-2011 e 2020-2021. Inclusão de internamentos por doença ativa ou por efeitos adversos de medicação usada no tratamento da DII. Potenciais fatores de prognóstico avaliados: tempo doença-internamento, duração do internamento, parâmetros analíticos à admissão, terapêutica prévia e realizada durante o internamento e desenvolvimento de complicações.

**Resultados:** Inclusão de 192 internamentos de 150 doentes (58.7% do sexo masculino), 60% com Doença de Crohn (DC) e 40% com Colite Ulcerosa (CU). Doença ativa foi o motivo de internamento em 187 (97.4%) dos casos e 5 (2.6%) ocorreram por efeitos adversos de medicação. Doentes com DC tinham menor idade ao diagnóstico ( $p=0.005$ ) e mais antecedentes cirúrgicos relacionados com a DII ( $p=0.021$ ). O número de reinternamentos diminuiu significativamente entre períodos ( $p=0.025$ ) enquanto que o uso de terapêutica biológica demonstrou uma evolução oposta ( $p<0.001$ ). A administração de transfusões sanguíneas durante o primeiro internamento evidenciou-se como potencial fator de prognóstico associado a reinternamentos ( $p=0.046$ )

**Conclusão:** Num período de dez anos, verificou-se uma diminuição dos efeitos adversos de medicação usada no tratamento da DII, uma diminuição dos reinternamentos e um aumento do uso de terapêuticas biológicas. A necessidade de transfusões sanguíneas parece ser um fator de risco associado a reinternamentos.

**Palavras-chave:** Doença inflamatória intestinal, Doença de Crohn, Colite Ulcerosa, Hospitalizações, Prognóstico.



## INTRODUCTION

Inflammatory bowel disease (IBD) is a group of immune-mediated disorders comprising Crohn's Disease (CD) and Ulcerative Colitis (UC)<sup>1</sup>. IBD shows its highest incidence and prevalence in Western Europe and North America. Its prevalence exceeds 0.3% in these countries and is rising globally<sup>2,3</sup>.

In Portugal, epidemiological studies are scarce, but have shown results in line with Western countries' epidemiology. Between 2003 and 2007, it was estimated that the prevalence of IBD increased from 86 to 146 patients per 100,000 inhabitants<sup>4</sup>. In addition, recent predictive models estimated that there will be an increase of 4-6 times in 2030<sup>5</sup>. Regarding incidence, the most recent data show a decrease from 54.9 to 48.6 per 100,000 over the period of 2017 to 2019<sup>6</sup>.

The natural history of IBD shows an unpredictable behavior of exacerbations and remissions. Exacerbations' severity can range from mild to severe or complicated forms, requiring long-term medication, hospitalizations and surgical treatment leading to enormous healthcare and economic costs<sup>7,8</sup>.

Several prognostic factors are associated with more complicated forms of the disease<sup>9,10</sup>. Regarding CD, clinical prognostic factors are: young age at diagnosis, smoking habits, disease location (ileal and ileocolic), involvement of the upper gastrointestinal tract or rectum, perianal disease and early presentation of stricturing or penetrating behavior<sup>9</sup>. Concerning UC, poor prognostic factors include early onset of disease, extensive illness and deep ulceration<sup>10</sup>.

Hospitalization and surgery rates are high in Europe. Nonetheless, recent studies show a downward trend in the last few years<sup>11,12</sup>. Multiple factors may contribute to this, including early diagnosis, clinical close monitoring and new therapeutic approaches<sup>12</sup>. However, potential explanations need to be clarified. Interestingly, in Portugal, between 2000 and 2015, there was an increase in the hospitalization rate for IBD, from 12.8 to 16.1 per 100,000 inhabitants<sup>13</sup>. Data also show that the hospitalization rate is higher for CD (11.2 per 100,000) which increased during this period, while the UC rate has remained stable (4.4-4.9 per 100,000)<sup>13</sup>.

As a matter of fact, IBD patients are increasingly being treated with biological therapies at an earlier stage<sup>14</sup>, but their influence on the course of the disease needs to be studied on a long-term basis. Literature supports that the use of immunomodulatory therapy reduces the risk of hospitalization and surgery for CD and hospitalization for UC<sup>15,16</sup>. However, the impact of biological therapy on these rates remains controversial and is still a matter of debate<sup>17-19</sup>.

In fact, there have been major changes concerning IBD, either epidemiological either related to patient management. Therefore, it is important to understand if the natural history of the disease is also changing.

This study aims to investigate the temporal evolution of IBD. We aim to identify epidemiological trends, especially in the most severe forms and analyze IBD-related hospitalizations to investigate putative differences regarding patients' characteristics and potential prognostic factors. These data may contribute to the optimization of medical and surgical approaches, with an impact on patient's quality of life and healthcare resource management.

## **METHODS**

### **Study Design**

This was a single center retrospective observational study in the Gastroenterology department of a tertiary hospital. Demographic, clinical, analytical and endoscopic data of patients admitted with IBD were reviewed. Clinical information was collected from patients' medical records.

The project was subjected to the standards of good clinical practice and always complied with the ethical precepts of the Helsinki's Declaration. The study was approved by the institutional ethics committee (CE-034/2023).

### **Study Population**

The study included adult patients, with IBD, admitted due to active CD or UC or in case of adverse events of therapies used to these conditions. The study periods comprised patients hospitalized from 2010 to 2011 and from 2020 to 2021.

Active disease was defined as presence of symptomatology attributed to IBD while adverse events were defined as clinical conditions reported and well-established as undesired effects of a therapy used for the treatment of CD or UC.

Patients hospitalized with IBD, but due to other concomitant conditions or electively admitted for endoscopic procedures were excluded. Patients with suspected IBD without diagnostic confirmation were also excluded.

### **Data Collection**

Demographic, clinical, analytical and endoscopic data were retrospectively obtained from hospital's database and from outpatient medical records when available.

Data collected included: gender, age (at diagnosis and on admission), family history of IBD, smoking habits, previous medications and therapy on admission, characteristics of CD and UC (extension, behavior, severity, and presence of complications), presence of extraintestinal manifestations, reason for admission, number of previous hospitalizations and history of IBD related surgeries.

Reason for admission was defined as the patient's main symptom on admission. Categories were created as followed: hematochezia, diarrhea, abdominal pain, fever, vomiting, fatigue and other (including leucopenia, inguinal pain and syncope).

Categories of patients regarding characteristics of CD and UC were generated according to Montreal's Classification<sup>20</sup> and endoscopic scores used were: simple Endoscopic Score for Crohn's Disease (SES-CD) and Mayo Endoscopic Subscore for UC.

In order to compare disease severity in both study periods, the following potential prognostic factors were assessed: time disease-hospitalization (defined as the time period from the moment of the diagnosis to the moment of the hospitalization), length of hospitalization (days), analytical parameters on admission (hemoglobin, leucocytes, platelets, C-reactive protein, albumin and creatinine), complications and therapy during hospitalization, surgery and development of colorectal carcinoma.

Our primary outcome were putative differences regarding patients' characteristics in the two study periods. Our secondary outcome was the study of prognostic factors responsible for rehospitalizations.

### **Statistical methods**

Data was analyzed with StataCorp LP® (version 16.0). Continuous variables were described with median and inter-quartile range (IQR) and categorical variables with frequencies or percentages.

Comparison of demographic and clinical characteristics of patients at baseline was performed with Mann-Whitney test, Fisher's exact test and Chi-2 test. Comparison of clinical variables between the two time periods was performed with Fisher's exact test and Chi-2 test. Univariate analysis of the factors associated with readmission was performed with logistic regression. A multivariate analysis to identify independent prognostic associated with multiple hospitalizations was performed with a logistic regression. Factors included in the multivariate analysis were those with a  $p < 0.2$  in the univariate analysis.

A  $p$ -value of  $< 0.05$  was considered statistically significant.

## RESULTS

After detailed analysis of hospitalizations in the considered periods, we included 192 hospitalizations from 150 patients (58.7% male), of whom 60% had Crohn's disease, and 40% Ulcerative Colitis. The median age at hospitalization was 39 years (IQR: 26-56). The median hospitalizations per patient was 1 (IQR 1-1) and the median length of hospital stay was 8 days (IQR 6-13). Demographic and clinical characteristics of the patients at baseline are summarized in **Table 1**. Globally, CD patients were significantly younger at diagnosis [median age: 25 years (IQR 20-27)] than UC patients [median age: 36.5 years (IQR: 25.5-49.75)] ( $p=0.005$ ). Additionally, CD patients had more episodes of IBD-related surgeries when compared to UC patients (42% and 17.9%, respectively) ( $p=0.021$ ).

**Table 1.** Demographic and clinical characteristics of patients at baseline

Characteristic	All (n=150)	Crohn's Disease(n=90)	Ulcerative Colitis (n=60)	<i>p-value</i>
Age at hospitalization (years) (IQR)	39 (26-56)	36.5 (24.75-56.25)	40 (31-57.50)	0.092
<b>Age at diagnosis (years) (IQR)</b>	<b>30 (21.75-47)</b>	<b>25 (20-47)</b>	<b>36.5 (25.5-49.75)</b>	<b>0.005</b>
Gender, n (%)				0.279
Male	88 (58.7%)	56 (62.2%)	32 (53.3%)	
Female	62 (41.3%)	34 (37.8%)	28 (46.7%)	
Montreal's classification, n (%)				
Age at diagnosis				
≤16 years (A1)		11 (12.2%)		
17-40 years (A2)		52 (57.8%)		
> 40 years (A3)		27 (30.0%)		
Location				
Terminal ileum (L1)		43 (47.7%)		
Colon (L2)		15 (16.7%)		
Ileocolon (L3)		32 (35,6%)		
Behavior				
Non-stricturing/Non-penetrating (B1)		31 (34.4%)		
Stricturing (B2)		34 (37.8%)		
Penetrating (B3)		25 (27.8%)		
Perianal Disease		20 (32.3%)		

Characteristic	All (n=150)	Crohn's Disease(n=90)	Ulcerative Colitis (n=60)	p-value
Disease extent				
Ulcerative proctitis (E1)			2 (3.3%)	
Left sided ulcerative colitis (E2)			12 (20.1%)	
Extensive ulcerative colitis (E3)			23 (38.3%)	
Unclassified			23 (38.3%)	
Extraintestinal manifestations, n (%)	19(12.7%)	12 (13.3%)	7 (11.7%)	0.764
Smoking habits, n (%)	21(14.1%)	16 (17.8%)	5 (8.5%)	0.110
Family history of IBD, n (%)	5 (3.3%)	3 (3.3%)	2 (3.3%)	1
<b>History of IBD-related surgeries</b>				
Yes, n (%)	34 (35.4%)	29 (42.6%)	5 (17.9%)	<b>0.021</b>
Number of previous IBD-related hospitalizations (IQR)	1 (0-2)	1 (0-2)	0 (0-2)	0.325

IBD: Inflammatory bowel disease, IQR: inter-quartile range

Indications for hospitalizations were as follows: 187 (97.4%) cases of active CD or UC and 5 (2.6%) cases of adverse events of therapies to these conditions. The therapy-related events included 3 (60%) acute pancreatitis secondary to azathioprine, 1 (20%) infectious esophagitis in a patient under methotrexate therapy and 1 (20%) case of leucopenia secondary to azathioprine. All cases of adverse events of therapies occurred in 2010-2011 period.

### Characteristics of hospitalizations by study period

The comparison between characteristics of hospitalizations in 2010-2011 and 2020-2021 is described in **Table 2**. The only statistically significant differences were the number of hospitalizations per patient and the use of biological therapy previous to the admission.

Concerning the number of hospitalizations per patient, there was an increase in patients with one hospitalization from one study period to the other (from 71.7% in 2010-2011 to 87.9% in 2020-2021) and the number of rehospitalizations decreased significantly (from 28.3% in 2010-2011 to 12.1% in 2020-2021) ( $p=0.025$ ). In the period of 2010-2011, 66 (71.7%) patients had one hospitalization, 21 (22.8%) had two, 1 (1.1%) had three and 4 (4.4%) had four hospitalizations. In 2020-2021, 51 (87.9%) patients had one hospitalization and 7 (12.1%) had two. There were no more than 2 hospitalizations per patient in this period.

The use of biological therapy previous to the admission increased in the second study period ( $p<0.001$ ). In 2010-2011, patients in 15.8% of hospitalizations were using biological therapy

previous to the admission: 10 (9.3%) Infliximab and 7 (6.5%) Adalimumab. Regarding the period of 2020-2021, its use was verified in 46.7% of hospitalizations: 7 (11.7%) Infliximab, 8 (13.3%) Adalimumab, 5 (8.3%) Ustekinumab, 7 (11.7%) Vedolizumab and 1 (1.7%) Tofacitinib. From those, in 7 (6.4%) hospitalizations patients were treated with combination therapy (5 azathioprine and 2 methotrexate) in 2010-2011 and 11 (18.3%) in 2020-2021 (10 azathioprine and 1 methotrexate).

No statistically significant difference was found in the number of hospitalizations per IBD type between the two study periods. In CD patients, the percentage of hospitalizations in 2010-2011 was 59.8% and 60.3% in 2020-2021. Regarding UC, the percentage of hospitalizations in 2010-2011 was 40.2% and 39.7% in 2020-2021. Overall, the percentage of hospitalizations was higher in CD patients than in UC patients in both periods.

Concerning characteristics of DC, in both periods, the most frequent age at diagnosis was between 17-40 years (A2) and behavior was stricturing (B2). The most frequent locations were terminal ileum (L1) and ileocolon (L3). Despite there being no statistical difference on SES-CD on admission, the score median decreased from 9 (IQR 4-24) in 2010-2011 to 7.5 (IQR 6-12) in 2020-2021. Regarding UC, the most frequent Mayo Subscore result on admission was 3.

As far as surgery is concerned, although no significant differences were found, there was a slight decrease in 2020-2021 and abdominal surgery was the most frequent in both periods.

No cases of colorectal carcinoma were found.

**Table 2.** Characteristics of hospitalizations by study period

<b>Characteristic</b>	<b>2010-2011 (n=127)</b>	<b>2020-2021 (n=65)</b>	<b>p-value</b>
Age (year) (IQR)	39 (29-55.5)	37 (25-60)	0.467
Males, %	63%	51.7%	0.17
Smoking habits, %	13.2%	15.5%	0.69
Family history of IBD, %	1.1%	6.9%	0.074
<b>Number of hospitalizations per patient</b>			<b>0.025</b>
1	71.7%	87.9%	
>1	28,3%	12.1%	
Disease			0.945
Crohn's Disease, %	59.8%	60.3%	
Ulcerative Colitis, %	40.2%	39.7%	
Characteristics of Crohn's disease (on admission), n			
Montreal's classification			
A (1,2,3)	7,42,27	6,22,9	0.154

Characteristic	2010-2011 (n=127)	2020-2021 (n=65)	p-value
L (1,2,3)	37,18,21	15,4,18	0.12
B (1,2,3)	27,31,18	11,13,13	0.279
Perianal disease, n	9	11	0.580
SES-CD on admission (IQR)	9 (4-24)	7.5 (6-12)	0.912
Characteristics of Ulcerative Colitis (on admission)			
Mayo score, n			0.689
1	1	1	
2	8	9	
3	26	18	
Therapy on admission, n			
<b>Biological therapy</b>	17	28	<b>&lt;0.001</b>
Corticotherapy	9	5	> 0.999
Time disease-first hospitalization (years)	4 (1-10,5)	4 (0-11)	0.871
Length of hospitalization (days)	8 (6-14)	8 (6-11)	0.783
Reason for admission, n			0.847
Hematochezia	7	1	
Diarrhea	42	26	
Abdominal pain	59	31	
Perianal complaints	3	1	
Fever	6	4	
Vomiting	4	1	
Fatigue	1	0	
Other	5	1	
Admission due to a therapy-related adverse event	5	0	0.169
Hemoglobin (g/dL) on admission (IQR)	11.7 (10.5-13.5)	11.9 (10.6-12.9)	0.777
Leucocytes (x10 <sup>9</sup> /L) on admission (IQR)	10.9 (7.8-14.2)	10 (7.9-12.9)	0.25
Platelets (x10 <sup>9</sup> /L) on admission (IQR)	352 (266-461)	358 (286-402)	0.95
C-reactive protein (mg/dL) on admission (IQR)	5.65 (1.83-11.9)	5.91 (2.03-12.87)	0.949
Albumin (g/dL) on admission (IQR)	3.3 (2.9-3.7)	3.35 (2.8-3.8)	0.962
Creatinine (mg/dL) on admission (IQR)	0.72 (0.63-0.94)	0.77 (0.7-0.88)	0.196
Complications during hospitalization, n			
Gastrointestinal hemorrhage	19	9	0.836
Anemia	29	22	0.102
Hypoalbuminemia	4	6	0.091
Acute Kidney Injury	4	4	0.447
Elevation of liver enzymology	2	0	0.550



Characteristic	2010-2011 (n=127)	2020-2021 (n=65)	p-value
Subocclusion symptoms	18	15	0.122
Abdominal fistula	19	9	0.836
Perianal abscess	4	4	0.447
Abdominal abscess	7	4	> 0.999
Peritonitis	3	1	> 0.999
Infections			
Herpes simplex virus	2	0	0.550
Cytomegalovirus	1	3	0.113
<i>Clostridioides difficile</i> colitis	4	1	0.166
Depressive symptoms	8	10	0.668
Antibiotherapy during hospitalization, n	79	38	0.463
Ciprofloxacin	57	27	0.437
Metronidazol	61	28	0.34
Corticotherapy during hospitalization, n	86	51	0.458
Supportive therapies during hospitalization, n			
Blood transfusions	6	4	0.736
Albumin	2	2	0.597
Iron infusion	12	10	0.237
Surgery, n			
Abdominal	12	10	0.237
Perianal	4	2	0.963

IBD: Inflammatory bowel disease; IQR: inter-quartile range; SES-CD: simple endoscopic score for Crohn's disease

### Potential prognostic factors associated with multiple hospitalizations

The univariate analysis of the potential prognostic factors associated with rehospitalization is described in **Table 3**. The only statistically significant difference was the administration of blood transfusions as supportive therapy during the first hospitalization ( $p=0.046$ ).

**Table 3.** Univariate analysis of potential prognostic factors associated with multiple hospitalizations

Characteristic	1 hospitalization (n=117)	>1 hospitalization (n=33)	p-value
Age (year) (IQR)	39 (26-55)	47 (28-60)	0.215
Males, %	60.7%	48.5%	0.345
Smoking habits, %	13.8%	15.2%	0.843
Family history of IBD, %	4.3%	0%	0.586
Disease			0.936
Crohn's Disease, %	59.8%	60.6%	

Characteristic	1 hospitalization (n=117)	>1 hospitalization (n=33)	p-value
Ulcerative Colitis, %	40.2%	39.4%	
Characteristics of Crohn's disease			
Montreal's classification, %			
A (1;2;3)	12.9%;61.4%;25.7%	10%;45%;45%	0.166
L (1;2;3)	50%;14,3%;35,7%	40%;25%;35%	0.369
B (1;2;3)	37.1%;35.7%;27.2%	25%;45%;30%	0.453
Perianal disease	29.3%	44.4%	0.442
SES-CD on admission (IQR)	6 (3-12)	12 (5-21)	0.577
Characteristics of Ulcerative Colitis			0.329
Mayo score, %			
1	5.3%	0	
2	36.8%	16.7%	
3	57.9%	83.3%	
Therapy on admission, %			
Biological therapy	28%	19.4%	0.337
Corticotherapy	8%	9.7%	0.721
Time disease-hospitalization (years) (IQR)	4 (0-11)	4 (1-10)	0.951
Length of first hospitalization (days) (IQR)	8 (6-12)	7 (5-15)	0.999
Complications during first hospitalization, %			
Gastrointestinal hemorrhage	15.4%	12.2%	0.785
Anemia	23.1%	36.4%	0.176
Hypoalbuminemia	5.1%	6.1%	>0.999
Acute Kidney Injury	2.6%	6.1%	0.303
Elevation of liver enzymology	0.9%	3.03%	0.393
Subocclusion symptoms	12.8%	24.2%	0.168
Abdominal fistula	12.8%	18.2%	0.409
Perianal abscess	4.3%	6.1%	0.649
Abdominal abscess	8.6%	-	0.118
Peritonitis	3.4%	-	0.576
Infections			
Herpes simplex virus	0.9%	-	>0.999
Cytomegalovirus	2.6%	-	>0.999
<i>Clostridioides difficile</i> colitis	3.9%	7.1%	0.523

<b>Characteristic</b>	<b>1 hospitalization (n=117)</b>	<b>&gt;1 hospitalization (n=33)</b>	<b>p-value</b>
Depressive symptoms	17.9%	14.3%	>0.999
Antibiotherapy during first hospitalization, %	63.7%	62.5%	0.9
Corticotherapy during first hospitalization, %	72.5%	78.8%	0.469
Supportive therapies during first hospitalization, %			
<b>Blood transfusions</b>	4%	16.7%	<b>0.046</b>
Albumin	3.2%	-	>0.999
Iron infusion	13.7%	8.7%	0.784

IBD: Inflammatory bowel disease; IQR: inter-quartile range; SES-CD: simple endoscopic score for Crohn's disease.

The multivariate analysis of the potential prognostic factors associated with multiple hospitalizations, including Montreal's Classification A ( $p=0.166$ ), subocclusion symptoms ( $p=0.068$ ), abdominal abscess ( $p=0.118$ ) and blood transfusions ( $p=0.046$ ), is described in **Table 4**.

**Table 4.** Multivariate analysis of potential prognostic factors associated with multiple hospitalizations

<b>Characteristic</b>	<b>OR</b>	<b>95% CI</b>	<b>p-value</b>
Montreal's Classification A	0.54	[0.21-1.41]	0.265
Subocclusion symptoms	0.61	[0.18-2.14]	0.392
Abdominal abscess	1	-	-
Blood transfusions	0.43	[0.03-5.44]	0.554

CI: confidence interval OR: odds-ratio

## DISCUSSION

The heterogeneity and high variability of IBD course represent a major challenge to understanding the impact of this disease in healthcare. In this study, based on a retrospective analysis of 192 hospitalizations from 150 IBD patients during the periods of 2010-2011 and 2020-2021, the temporal evolution of IBD in a gastroenterology department of a tertiary hospital is reported. This analysis found differences regarding the number of hospitalizations per patient and the use of biological therapies previous to the admission. Additionally, it was found that the necessity of blood transfusions as a supportive therapy during the first hospitalization may be a potential prognostic factor associated with readmission.

The number of patients with more than one hospitalization decreased significantly from one study period to the other. These results are in accordance with what has been reported in the most recent Portuguese studies. Between 2010 and 2015, Dias *et al.*<sup>13</sup> reported an increase in the hospitalization rate of IBD, while Santiago *et al.*<sup>21</sup> reported a decrease of 2.5 times in IBD-rehospitalization rate per 100 000, between 2003 and 2015.

In parallel to this difference, an increase in the use of biological therapies before the admission was verified in 2020-2021. This fact is consistent with the changes observed in IBD patients' management in recent years, showing that patients are initiating biological therapy increasingly earlier after the diagnosis<sup>15,16,22</sup>. Several studies have tried to demonstrate the impact of these therapies on hospitalizations and surgery rates. In the Epi-IBD study, Burisch *et al.*<sup>15,16</sup> demonstrated that immunomodulatory therapy reduces the risk of hospitalization for IBD patients. However, the results regarding biological therapies have been controversial. Concerning tumor necrosis factor antagonists (anti-TNF), studies have shown that Infliximab and Adalimumab are associated with fewer hospitalizations and surgery<sup>18,23</sup>. Moreover, Magro *et al.*<sup>17</sup> in a systematic review and meta-analysis also corroborate that Infliximab reduces both. Nevertheless, a recent Canadian study failed to prove the expected declines in hospitalizations and intestinal resections for IBD patients under anti-TNF therapies<sup>19</sup>.

Specifically concerning surgery, in line with the controversy discussed above, in this study, no significant difference was found, which could mean that it remained stable between the periods studied. Unfortunately, results were not statistically different according to subgroups (CD and UC). However, it was found that CD patients had more previous IBD-related surgeries. In fact, these findings are in accordance with previous works<sup>12</sup>. Furthermore, only 1/5 of CD patients develop perianal disease and this also leads to a higher risk of resections and hospitalizations<sup>24</sup>.

Biological therapies have demonstrated high efficacy in the induction and maintenance of disease remission and mucosal healing<sup>18,25</sup>. Moreover, it is recognized that combination

therapy (with azathioprine, methotrexate or mercaptopurine) contribute to the optimization of medical approach with superior outcomes<sup>26,27</sup>. The use of these therapies may also be responsible for the occurrence of adverse events<sup>28</sup>. Nevertheless, this analysis revealed that hospitalizations due to adverse events of IBD-related therapies were very low and registered only in the 2010-2011 period. A possible explanation could be that the majority of adverse events of these therapies are mild and do not require hospitalization. Supporting this possible explanation is a systematic review and network meta-analysis of Wheat *et al.*<sup>29</sup>, who reported that IBD patients under biologics have no significant increased risk of severe infections.

This work revealed that the percentage of hospitalizations was higher for CD patients than for UC patients in both periods, despite not being statistically different. These data are in agreement with the results of previous studies conducted in Spain, between 1997 and 2012<sup>30</sup> and in Portugal between 2010-2016<sup>13</sup>.

Anemia was also a common complication found during hospitalizations in both study periods, explaining the frequent use of iron and blood transfusions as supportive therapies. This is in accordance with Filmann *et al.*<sup>31</sup> who reported anemia as a prevalent complication of IBD, in particular in patients with active disease and under IBD-specific medication. Furthermore, in a USA nationwide study, anemia was identified as a factor associated with hospitalizations in patients admitted to the emergency department<sup>32</sup>. This reinforces the importance of an early diagnosis of this condition and optimization of medical approaches as it may be related to the severity of the disease and have an impact on the prognostic and management of these patients. In fact, regarding potential prognostic factors, we reported that the administration of blood transfusions was associated with risk of multiple hospitalizations. This was in accordance with Mudireddy *et al.*<sup>33</sup>, which demonstrated that blood transfusion at first admission was associated with an increased risk of readmission at 1 and 3 months. In addition, Micic *et al.*<sup>34</sup> reported an association between blood transfusions and an increased risk of readmission in CD patients and patients submitted to surgical procedures. In fact, the need for blood transfusions may be indicative of more severe forms of the disease, which possibly explains its association with hospitalizations and readmissions.

Several studies have tried to demonstrate predictors and risk factors associated with rehospitalizations, but studies conducted in Europe and Portugal are scarce<sup>21,33-35</sup>. A recent retrospective analysis of all Portuguese hospital IBD-related discharges of Santiago *et al.*<sup>21</sup> found younger age (<20 years old), ileostomy, penetrating disease and perianal disease in CD patients and large intestinal resection, colostomy, and smoking habits in UC patients as factors associated with increased risk of rehospitalizations. However, in the present study, these potential prognostic factors did not show statistical significance.

The major strength of this study is the extended length of time (10 years) between comprised periods, allowing to investigate the temporal evolution of IBD. Nonetheless, this study has some limitations. Firstly, its retrospective design may lead to a possible bias in the selection of patients and difficulties in collecting complete clinical information. As an example, it may not have been feasible to classify the full extent of UC in all patients, as some patients did not undergo a complete colonoscopy. Secondly, this study only included patients from a single center.

In the future, prospective multicenter studies are needed to clarify these findings and the impact of biological therapy on the IBD disease course.

## **CONCLUSION**

In conclusion, this study showed differences in IBD-related hospitalizations and patients' characteristics between 2010-2011 and 2020-2021. A decrease in IBD-related therapies' adverse events, a decrease in IBD-related rehospitalizations and an increase in the use of biological therapies were verified. However, the impact of these therapies on the course of the disease and hospitalization and surgery rates remains unclear.

This study also revealed that the necessity of blood transfusions during the first hospitalization may be a potential prognostic factor associated with readmission.

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