



Original Article

Postoperative mortality in inflammatory bowel disease patients



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ABSTRACT

Introduction: Since the 1960s, mortality in Crohn's disease and Ulcerative Colitis patients had a significant decrease due to advances in medical and surgical therapy. An important proportion of these patients are submitted to surgical procedures during their disease course, with postoperative mortality between 4 and 10%.

Methods: 157 inflammatory bowel disease patients submitted to surgical therapy were retrospectively identified and allocated in 2 groups (Crohn's and colitis). Deaths were individually discriminated in detail.

Results: 281 surgical procedures were performed. In the colitis group, 43 operations were performed in 24 patients; in the abdominal Crohn's subgroup, 127 procedures in 90 patients and in the perineal Crohn's subgroup, 115 in 64 patients, respectively. Nine postoperative deaths were observed (3 in the colitis and 6 in the Crohn's groups). Overall postoperative mortality was 5.7% (4.5% for Crohn's; 6.6% in abdominal Crohn's and 12.5% for Colitis). Most of deaths were related to emergency procedures and previous use of corticosteroids. The cause of death in all patients was sepsis.

Conclusions: Overall postoperative mortality in inflammatory bowel disease was 5.7%, and it was attributed to the severity of the cases referred.

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Mortalidade em portadores de doença inflamatória intestinal submetidos a tratamento cirúrgico

RESUMO

Introdução: A partir da década de 60, a mortalidade dos portadores de doença de Crohn (DC) e a Retocolite Ulcerativa Inespecífica (RCUI) teve declínio devido a novas terapêuticas clínicas e cirúrgicas. Importante proporção destes pacientes é submetida a procedimentos cirúrgicos no decorrer das suas vidas, com taxas de mortalidade variando entre 4 e 10%.

Palavras-chave:

Mortalidade

Doença de Crohn

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Retocolite ulcerativa
Cirurgia

Método: Foram identificados retrospectivamente 157 pacientes portadores de doenças inflamatórias intestinais (DII), submetidos a operações abdominais ou perineais, divididos em dois grupos (DC e RCUI). Os casos de óbitos foram discriminados e avaliados individualmente, de forma descritiva.

Resultados: 281 operações foram realizadas. No grupo RCUI foram realizadas 43 operações em 24 pacientes, no subgrupo DC abdominal, 127 operações em 90 pacientes e no subgrupo DC perineal, 115 em 64 pacientes, respectivamente. Do total de 9 óbitos, 3 ocorreram no grupo RCUI e 6 no DC. A mortalidade geral nas DII foi de 5,7%. Para a DC, 4,5%. No subgrupo de operações abdominais foi de 6,6% e para a RCUI 12,5%. A maior parte dos óbitos estavam relacionados a procedimentos de urgência/emergência, com uso prévio de corticoterapia. A causa mortis em todos os pacientes foi sepse.

Conclusões: A taxa de mortalidade cirúrgica nas DII foi de 5,7%, atribuídas pela severidade dos casos.

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Introduction

Crohn's disease (CD) and Ulcerative Colitis (UC) present a not homogeneous and increasing global incidence over the years. Due to the heterogeneous demographic character among countries, the incidence of UC varies between 8–14/100,000 and 120–200/100,000 people; on the other hand, the incidence of CD varies between 6–15/100,000 and 50–200/100,000.¹

From the 1960s onwards, the mortality of patients with these diseases, mainly UC, showed a significant decline due to the use of new clinical and surgical therapeutic measures.² In the case of CD, there is a low risk, but the risk of death is higher *versus* general population (considering individuals of the same age and gender). A meta-analysis pointed to a downward trend in mortality rates over the last 30 years, but without statistical significance.³ In UC, another meta-analysis showed that the total mortality of patients did not differ from the general population, although in subgroups of patients with a more severe and extensive disease (and that consequently made use of immunosuppressive medication) the risk of death was higher.⁴

A significant proportion of patients with inflammatory bowel disease (IBD) will undergo surgical procedures throughout their lives. In CD, bowel surgery is needed in about 70–80% of cases after 20 years of illness. Of these patients, about 30% will require a second surgery after 10 years.¹ In patients with UC, colectomies are required in approximately 20–30% of patients after 25 years of disease.¹ Considering the whole range of operative procedures, intestinal resections in patients with IBD performed on an emergency basis are associated with higher mortality rates. In addition to the increased risk due to the urgency required *per se*, at the time of surgery, many patients are malnourished and in the use of drugs such as corticosteroids, immunosuppressants and biological agents, which may have an impact on morbidity and mortality.⁵

The use of tumor necrosis factor alpha (anti-TNF α) inhibitors has altered the natural history of the disease. In randomized studies, the reduction of complications and of the need for surgery has already been demonstrated. On the other hand, in populational studies, this has not yet been documented.⁵

The primary objective of this study was to determine the mortality rate among patients with IBD in a referral service for the management of CN and NSUC patients undergoing surgical procedures. The secondary objectives were to describe the demographic characteristics of this population, as well as to make a detailed evaluation of the cases of death, relating them to possible risk factors.

Method

This study was approved by the Research Ethics Committee of the Bioethics Nucleus of the Pontifícia Universidade Católica do Paraná (PUC-PR), according to the Presentation Certificate for Ethical Appreciation (CAAE) number 58325916.6.0000.0020, provided by the *Plataforma Brasil* website..

This was a retrospective, analytical and longitudinal study of a series of cases. 157 patients submitted to surgical procedures related to IBD from January 2004 to December 2014 in a referral service were identified. These patients were divided into groups according to the diagnosis (UC and CD). The CD group was further divided into two subgroups: abdominal procedures and perineal procedures. After reviewing the patient's medical records, the following variables were analyzed: age, gender, indication of surgery, procedure performed, the system of designation of the procedure (elective or urgent) and death in the postoperative period. Previous treatments (clinical and surgical ones) and in particular the use of corticosteroids and anti-TNF α agents were analyzed. The occurrence of malnutrition (defined as a serum albumin value below 3.0 mg/dL), use of total parenteral nutrition, anemia (defined as a hemoglobinemia [Hb] <8 g/dL), and the need for blood transfusion were equally checked. The type of surgery performed and the pre-operative hospitalization time were also analyzed. The cases of death were individually discriminated and evaluated. Surgical procedures not related to IBDs were excluded from the analysis.

Results

157 patients (90 males and 67 females) submitted to a total of 281 operations (43 in patients with UC and 238 in patients with

Table 1 – Distribution of patients in relation to gender and disease, with numbers of patients operated by group.

	Crohn's disease (CD)		Ulcerative colitis (UC)		Total
	Male	Female	Male	Female	
Patients (n)	75	58	15	9	157
Surgical procedures (n)	135	104	27	16	281
Mean age	34.2 (12-65)	41.5 (15-82)	37.7 (19-76)	40.6 (14-64)	36.2 (12-82)

CD) were analyzed. The mean age was 36.2 years. These data are detailed in [Table 1](#).

In the UC group, 43 operations were performed in 24 patients. The mean number of surgical procedures per patient was 1.79 (1-4). The types of operations and their indications are listed in [Table 2](#). As observed, among the procedures, 17 were performed on an emergency basis. The elective surgical indications were: refractory disease, intestinal transit reconstruction, dysplasia-associated lesion or mass (DALM), and stenosis. The surgical indications of emergency were: disease refractory to medical treatment, abdominal abscess or collection, toxic megacolon, intestinal obstruction, and evisceration. The most common surgical indication – both for elective surgery and for emergency surgery – was refractoriness to medical treatment. In this group, 3 deaths occurred. Still, in this group, the mortality rate of total colectomy with end ileostomy in the emergency room reached 30%.

In the group of patients with CD, 238 operations were carried out in 133 patients (mean age of 35.6 years; [Table 3](#)). In 7 cases, abdominal and perineal procedures were performed during the same surgical time. The mean number of surgeries per patient was 1.4 (1-5). In the abdominal CD subgroup, 32 operations were carried out on an emergency basis. Surgical indications in patients with CD were, among others: localized ileocolic disease, stenoses, fistulas, refractoriness to medical treatment, perineal disease, intestinal obstruction, an abdominal collection or anastomotic dehiscence, intestinal perforation, evisceration, stoma necrosis, hemorrhage, abdominal wall/peristomal abscess, and bladder fistula. The most common indication in elective procedures was stenosis; on the other hand, in the emergency surgeries, the most common indication was abdominal collection/anastomotic

dehiscence ([Table 3](#)). There were 6 related deaths in the abdominal CD subgroup.

In the group of patients operated on for CD, 115 perineal operations were performed in 64 patients (perineal CD subgroup): 39 men (mean age 36 years) and 25 women (mean age 31.9 years). The mean number of procedures per patient was 1.79 (1-8 procedures per patient). 101 fistulotomies and 19 other procedures (drainage of abscess, anal dilatation, debridement, and fissurectomy) were carried out. There were no deaths in this subgroup.

Among the patients analyzed, 9 deaths were identified, 3 (1 male and 2 female) in the UC group and 6 (4 male and 2 females) in the CD group. The mean age of the cases of death was 37.3 (14-77) years. The overall mortality rate was 5.7% (9/157 patients). For the CD group, the mortality rate was 4.5% (6/133 patients); in the subgroup of abdominal operations the mortality rate was 6.6% (6/90 patients operated), and in the UC group, 12.5% (3/24 patients operated). These data are detailed in [Table 4](#).

The 9 patients who died had undergone 27 operations (1-6 procedures). In only two cases, only one operation was performed during hospitalization. Among these surgeries, as a main procedure 6 colectomies (with or without enterectomy), three enterectomies, three perineal procedures, and 15 procedures of other types were performed ([Table 5](#)).

In the 3 UC-related deaths, the disease had a pancolitis presentation. All of these patients underwent intravenous (IV) corticosteroid therapy, one of them had been taking oral mesalazine for less than a week, another had used azathioprine, and the third had undergone a single-dose infusion of infliximab two days before surgery. None of these patients had any previous surgery related to IBD. All were submitted

Table 2 – Procedures performed and regimen of surgical indication in patients with UC.

Surgical procedures performed	Elective	Emergency	Total
Total colectomy with terminal ileostomy	2	9	11
Total proctocolectomy with ileal pouch	6	0	6
Total proctocolectomy with end ileostomy	4	0	4
Proctectomy	3	0	3
Right colectomy	2	0	2
Total colectomy with ileorectal anastomosis	1	0	1
Enteroanastomosis	8	0	8
Laparotomy for abdominal collection drainage	0	3	3
Laparotomy for lysis of adhesions	0	2	2
Abscess drainage by perineal route	0	1	1
Peristomal abscess drainage	0	1	1
Abdominal wall reconstruction	0	1	1
Total	26	17	43

Table 3 – Procedures performed and regimen of surgical indication for surgeries in patients with CD (abdominal subgroup).

Surgeries performed	Elective	Emergency	Total
Enterectomy and/or stenoplasty	39	3	42
Right ileocectomy	32	2	34
Right ileocectomy with Enterectomy	22	0	22
Left colectomy	5	0	5
Total colectomy with end ileostomy	3	2	5
Total proctocolectomy with end ileostomy	3	0	3
Proctectomy	2	0	2
Enteroanastomosis	6	0	6
Ileostomy	4	4	8
Loop colostomy	0	2	2
Colorrhaphy	4	0	4
Exploratory laparotomy	0	11	11
Urological procedures	3	3	6
Reconstruction of the abdominal wall	0	3	3
Peritoniotomy	0	3	3
Incisional herniorrhaphy	1	0	1
Oophorectomy	1	0	1
Total	126	32	158

Table 4 – Mortality rate in relation to the number of patients and operations performed in the different groups.

	Patients	Operations	Deaths	Mortality (%)	
				Patients	Operations
General	157	281	9	5.7	3.2
Crohn's (abdominal subgroup)	90	127	6	6.6	4.7
Crohn's (perineal subgroup)	64	115	0	0	0
UC	24	43	3	12.5	6.9

to an emergency surgery. The three cases had as an indication of the procedure a toxic megacolon, and in one case colonic perforation was present.

Between CD-related deaths, the disease was localized to the small intestine in two cases (one of which had an associated perineal disease); two other patients suffered from colonic and perineal disease; in one of the cases, the disease was located in the small bowel, colon, and perineum; and in the latter case only an ileocolic disease was diagnosed. Only one patient was not operated on an emergency basis. Only two patients were not in use of preoperative corticosteroids.

One patient had been treated with intravenous corticosteroid therapy and underwent a perianal abscess drainage procedure under diagnostic suspicion of CD only five days before a total colectomy with emergency ileostomy due to colonic perforation and a low digestive hemorrhage. Only one patient was in use of biological drugs before surgery: adalimumab, already in long-term use, associated with azathioprine and oral corticosteroid therapy, also for a long time. In this patient, the indication for surgery was due to multiple enterocutaneous (peri-ileostomic) fistulas, in an elective procedure.

In all the deaths a blood transfusion was indicated (one patient underwent transfusion reaction, with the suspension of the transfusion), with the presence of malnutrition at some time of the hospitalization. In only one case the patient did not receive total parenteral nutrition.

In all patients, the cause of death was sepsis, four of pulmonary origin and two cases of central venous catheter, in

addition to one of abdominal focus, fungal systemic, and a progression of Fournier's syndrome, respectively (Table 5).

Discussion

Among patients with CD, intestinal surgery is required in about 70–80% of cases after 20 years of illness. In patients with UC, colectomies are required in approximately 20–30% of patients after 25 years of disease.¹ Frolkis et al., in a meta-analysis of population studies, have identified that the risk of surgery at 1, 5, and 10 years after the diagnosis of CD and between 1 and 10 years after the diagnosis of UC has decreased significantly over the last six decades.⁶

A Danish study observed increased mortality in cases of UC in patients older than 50 years, during the first two years after diagnosis, and in patients with an extensive colitis. Such deaths usually occur in the perioperative period in patients with severe disease.⁷ Kaplan et al. assessed the post-colectomy mortality in patients with UC, and also identified the occurrence of higher mortality in patients over 60 years of age.⁸ In the present study, all deaths related to UC had a recent diagnosis of disease (<2 years) and suffered from pancolitis. Only one of the deaths related to UC occurred among patients aged over 60, but proportionately this increase in mortality was also identified.

In the same publication above mentioned, Kaplan et al. found a mortality rate ranging from 2.3% to 7.4% of the cases (general mortality, and in patients submitted to a complete

Table 5 – Detailed analysis of cases of death.

	Gender	Age	AZA	MSZ	CTC	Anti-TNF- α	Surgeries	Previous treatments			Indication	Emergency	POHT (days)	Surgeries (n)	Causa mortis	
								Malnutrition/TPN	Anemia/Transfusion	Surgery performed (initial)						
CD	1	M	38	Yes	No	No	No	Enterectomy	Yes/Yes	Yes/Yes	Enterorrhaphies and ileostomy	Enterocutaneous fistulas	Yes	11	4	Abdominal sepsis
	2	M	31	Yes	No	Yes	No	No	Yes/Yes	Yes/No	Debridement	Fournier's Sd.	Yes	0	6	Fournier's Sd.
	3	F	77	Yes	Yes	No	No	No	Yes/Yes	Yes/Yes	Right ileocectomy and enterectomy	Enterocutaneous fistulas	Yes	4	2	Pulmonary sepsis
	4	M	44	Yes	No	Yes	No	Right ileocectomy	Yes/Yes	Yes/Yes	Right ileocectomy	Intestinal occlusion	Yes	1	2	Pulmonary sepsis
	5	M	18	No	No	Yes	No	Perianal abscess drainage	Yes/Yes	Yes/Yes	Total colectomy with end ileostomy	Colon perforation + LDH	Yes	0	6	Central venous catheter sepsis
	6	F	20	Yes	No	Yes	Yes (ADA)	Two-stage total colectomy and fistulotomy	Yes/Yes	Yes/Yes	Two-stage enterectomy and fistulotomy	Enterocutaneous fistulas	Yes	2	3	Central venous catheter sepsis
NSUC	7	F	18	Yes	Yes	Yes	No	No	Yes/Yes	Yes/Yes	Total colectomy with end ileostomy	Intractability – hemorrhage	Yes	17	1	Fungal sepsis
	8	F	14	Yes	Yes	Yes	Yes (IFX)	No	Yes/Yes	Yes/Yes	Total colectomy with end ileostomy	Intractability – perforation	Yes	3	2	Pulmonary sepsis
	9	M	76	No	No	Yes	No	No	Yes/No	Yes/Yes	Total colectomy with end ileostomy	Intractability – toxic megacolon	Yes	1	1	Pulmonary sepsis

M, male; F, female; AZA, azathioprine; MSZ, mesalazine; CTC, corticosteroids; TPN, Total parenteral nutrition; POHT, Pre-operative hospitalization time; n, number; HDB, low digestive hemorrhage; IFX, infliximab; ADA, adalimumab; Sd., syndrome.

colectomy with end ileostomy and the closure of the rectal stump, respectively).⁸ In the present study, we identified in the UC group a general mortality of 12.5%, but that reached 30% in those patients submitted to this same procedure also on an emergency basis. Still, according to the same authors, a higher mortality rate was also observed in patients operated after 6 days of hospital admission.⁸ These data were also registered in another Canadian study, where the authors noted that the complication rate and mortality were higher in patients submitted to emergency colectomies, in cases where the surgery was performed 14 days after hospitalization (in comparison to patients with their surgery performed between 3 and 14 days).⁹

Another factor to consider is the number of colectomies/year for UC treatment, considered as of small (<4 colectomies/year), medium (4–11) and large (>11 colectomies/year) volume. Mortality was higher in hospitals with a small volume of surgeries.⁸ Our study presented a small volume (1.4) of annual colectomies in the initial study period (2004–2010), but that reached a medium volume (4) in its final period (2011–2014). Therefore, the UC management experience is directly linked to complications and deaths in this difficult patient population.

Undertaking a colectomy in isolation in patients with UC is not a usual treatment. However, in the present study, this scenario occurred on two occasions: in a case of a patient already submitted to a left colectomy, with a transverse colon stoma and closure of rectal stump in an emergency basis due to hemorrhage, and in another patient to whom the surgical indication was due to a dysplastic lesion in the right colon, with the refusal of the patient to perform a wider colectomy.

In CD, the surgical mortality reported in some series ranges from 0.5% to 5%,^{10,11} a number similar to our 4.5% found in the group of Crohn's patients operated on in our sample.

Due to its potential immunosuppressive effect, the use of biological drugs has always been much questioned regarding the increase of postoperative complications, especially those of the infectious type. In this sense, several publications dealt with the theme. In a meta-analysis and systematic review, a slight increase in postoperative complications associated with their use was observed, particularly in CD patients.¹² On the other hand, another Danish study found that the use of infliximab in the preoperative period did not increase morbidity and mortality rates,¹³ which was also confirmed in two other relevant prospective studies.^{14,15} In the present series, only 2 patients who died had been medicated with biological agents in the preoperative period (1 in CD and 1 in UC), both with the associated use of corticosteroids.

Corticosteroid therapy has also been extensively studied. Despite its undeniable beneficial effects in the treatment of IBDs, especially in the acute phase, its postoperative repercussion is negative. TREAT¹⁵ and ENCORE¹⁶ studies identified a potential risk for infectious postoperative complications and deaths in association with corticosteroid use. Another large Canadian study also found this association, with an increase in postoperative complications but not in mortality.¹⁷ In this series, we identified this risk factor in all UC-related deaths and in 2/3 of CD-related deaths.

Anemia was also an important factor identified in cases of death. All patients had levels of Hb <8 g/dL at some time

during hospitalization. A Korean study cites a hematocrit (HT) <30% as a risk factor for early postoperative complications.¹⁸ In a retrospective study on post-bowel resection morbidity in CD cases, Bruewer et al. found that patients with Hb <10 g/dL showed a significant association with postoperative septic complications, compared with patients with Hb >10 g/dL, in a proportion of 20% versus 6%, respectively ($p < 0.05$).¹⁹

Another determinant risk factor for postoperative morbidity and mortality is the nutritional status of the patient. In a series comparing anastomosis with manual or mechanical suture, Smedh et al. observed that the complication rates were lower in the group previously treated with an enteral diet before the procedures.²⁰ In addition, a Korean study found that serum albumin levels below 3 g/dL are predictors of increases in complications and that its preoperative correction decreases morbidity rates.¹⁸ Yamamoto et al. also identified hypoalbuminemia (<3 g/dL) as a risk factor for postoperative abdominal septic complications in cases of CD.¹¹ This risk factor was detected even more severely (albumin <2 mg/dL) in all deaths studied in this series.

Our study presents significant limitations, which must be taken into account in the analysis of the results. Firstly, this is a series of retrospective, descriptive cases, without comparison among groups and without statistical analysis, and which had the simple objective of serving as an alert for the seriousness of the surgical treatment of IBD in our country. In addition, the high number of mortality cases demonstrates the clear bias of a referral center in the management of these diseases, which receive severe, often late, cases – which increases complications. Despite its limitations, it should be noted that this is the first descriptive analysis on mortality in IBD cases in our country.

In summary, the overall mortality rate found in the present study was 5.7% of the patients. The presence of several risk factors acting simultaneously and in a complex way contributed to the postoperative mortality in cases of IBD in the group of deaths evaluated here. Among the main risk factors found, there is the emergency and urgency regimen, multiple operations, malnutrition, anemia, and previous corticosteroid therapy. Studies with a greater number of patients are needed, in order to obtain a deeper understanding of postoperative mortality in the management of IBDs in our scenario.

Conflicts of interest

PGK: Abbvie, Ferring, Janssen, Pfizer, and Takeda; EFM: Abbvie and Janssen. The other authors declare no conflicts of interest.

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