

## Predictive Factors of Mortality in Ischemic Colitis in a Serie of Hospitalized Patients

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### Abstract

**Objective:** To analyze the outcome of patients diagnosed of Ischemic Colitis to identify predictive factors of mortality.

**Design:** Retrospective analysis of hospitalized patients in a single center.

**Material and Methods:** Patients were selected between January 1988 to December 2015, at the emergency department with Ischemic Colitis (IC) or who suffered an episode after admission due to another cause, Data was collected from the electronic history records of the hospital. Patients were identified by the international classification disease (ICD-10). We assessed the association between patient's characteristics and mortality. Variables with an independent influence on mortality were identified by stepwise regression analysis.

**Results:** 286 patients were included; mean age  $76 \pm 11$  years (range: 28 - 101 years). Ischemic Colitis localized in left colon was presented more frequently as mild-moderate abdominal pain (120 cases; 56.6%) ( $p = 0.032$ ) and lower intestinal bleeding (134; 63.8%) ( $p = 0.001$ ). Presentation as severe abdominal pain were highly frequent in IC localized in right colon (27; 69.2%) and in patients with pancolitis (28; 76.6%), but it was significantly less frequent in cases localized in left colon (42; 20%) ( $p = 0.001$ ). A total of 190 patients (66.4%) were managed with non-surgical treatment and 96 (33.6%) cases underwent surgery. Death happened in 50 patients (17.5%), 28 (29.1%) among those underwent surgery and in 22 (11.5%) with conservative treatment ( $p = 0.001$ ). The presence of abdominal pain was the main predictive factor. Abdominal pain increases the risk of death 17.9 times (95% CI: 2.25 - 142.38). Patients with ischemic colitis of the right side had a higher mortality than those with involvement of the left colon (95% CI: 1.065 - 4.85).

The presence of bleeding was analyzed as a protective factor, so the risk of death reduced by 0.4 times (95% CI: 0.201 - 0.890).

**Conclusion:** Ischemic Colitis is associated with high elevated mortality. Patients with exclusive involvement of the left colon and intestinal bleeding clinic have a better prognosis and reversible form of this pathology. Patients with right colon involvement or pancolitis progress more frequently to the irreversible form of HF with necrosis and intestinal gangrene.

**Keywords:** Ischemic Colitis; Intestinal Ischemia; Lower Intestinal Bleeding; Non-Occlusive Intestinal Ischemia

### Abbreviations

IC: Ischemic Colitis; CT: Computerized Tomography; SMA: Superior Mesenteric Artery; IMA: Inferior Mesenteric Artery

## Introduction

Ischemic colitis (IC) happens when colonic blood flow cannot maintain metabolic needs of colon causing ischemic injury [1-3]. It constitutes one of the most common causes of intestinal ischemia and one of the most common causes of gastrointestinal bleeding [4].

In the last few years there has been a special inter-metastatic pathology, both in terms of prospects and clinical aspects. Ischemic colitis presents an annual incidence of 4.4 to 44 per 100,000 cases [5]. Furthermore, three of every 1000 hospital admissions at one tertiary care center in the United States were for ischemic colitis [6]. A population-based study from the Mayo Clinic reported an incidence rate of 16 cases per 100,000 person-year when adjusted for gender and age, and further demonstrated that the incidence has been increasing over the past ten years [2].

Aetiology is multifactorial and frequently the exact cause remains unclear. It has been described in younger patients, related to other conditions, such as drug users, oral contraceptives or coagulopathies [3,7,8].

High index of suspicion for diagnosis, implementation of medical supportive care and prompt surgical intervention are required for these patients to have a favorable evolution [3]. In this article, we describe the characteristics and outcome of patients diagnosed of IC and hospitalized in a single tertiary center. The primary outcome was to identify predictive factors of mortality in patients who were hospitalized for IC or who suffered an episode of HF after admission. For this purpose we studied all the cases of IC treated in our center during 27 years, a total of 286 cases were collected and analyzed.

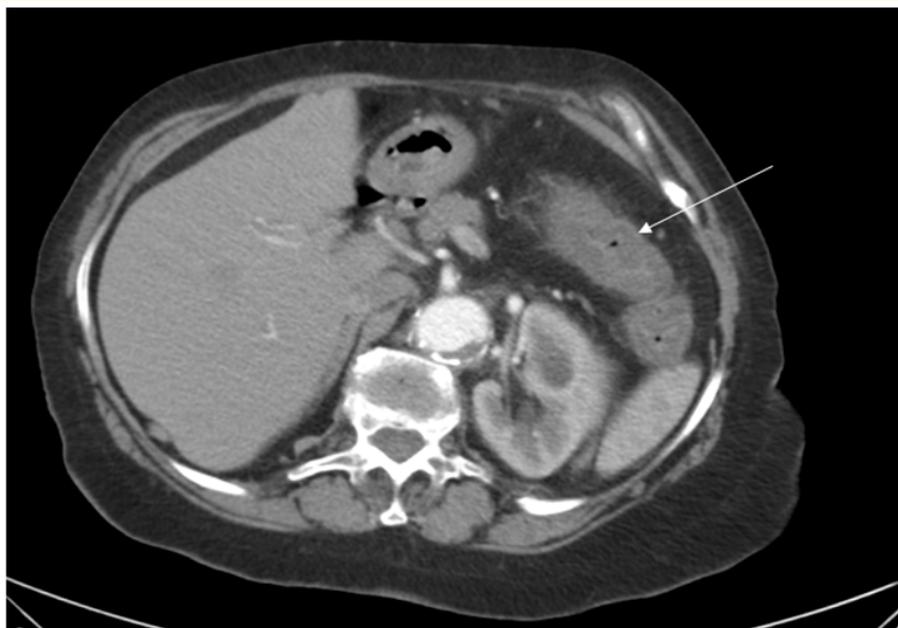
## Material and Methods

### Study design

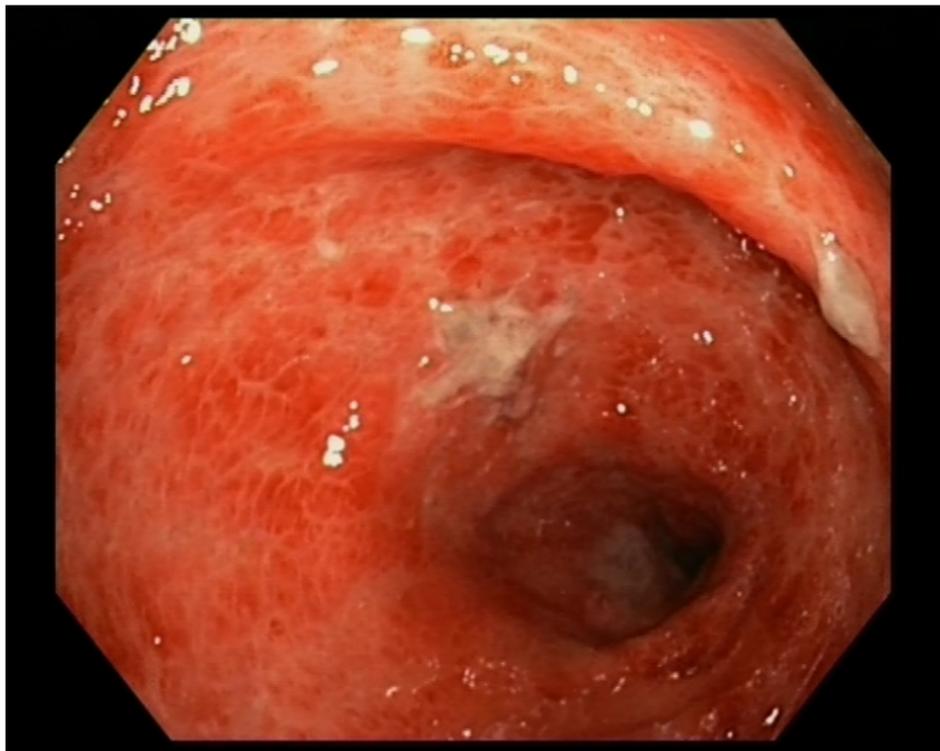
This is a retrospective analysis of all patients diagnosed of IC treated at Prince of Asturias Teaching Hospital, in Madrid, Spain, from January 1988 to December 2015.

### Patient selection

A review was performed of consecutive patients who were diagnosed of IC, admitted at the emergency department, or who suffered an episode of IC after admission for another cause, between January 1988 to December 2015. Data were collected from the electronic history records of the hospital. Patients were identified by the international classification disease codes (ICD-10), selecting the code K55 for intestinal vascular disorders of the intestine. 960 possible cases were identified. Clinical histories were reviewed individually to exclude misdiagnosis. Inclusion criteria was diagnosis of IC, in patients with signs and symptoms suggestive of IC and clearly defining findings in CT or colonoscopy or surgical specimens.



**Figure 1:** Ischemic colitis affecting transverse and left colon.



**Figure 2:** Endoscopic vision of ischemic colitis.

Computed tomography criteria of IC included: bowel wall thickening, thumb printing, and pericolic fat stranding [3] (Figure 1). Endoscopic findings of IC were mucosal edema with haemorrhagic infiltration and/or superficial ulcers or bluish discoloration of the mucosae with deep ulcers (Figure 2). Histological study suggestive of IC included loss of epithelium, edema of mucosae and fibrosis in the deeper layers [9,10].

Exclusion criteria were infectious or inflammatory colitis, acute or chronic mesenteric ischaemia, ischaemic colitis due to trauma or mechanical causes and all those cases that failed to comply with the diagnostic criteria of ischaemic colitis or the diagnosis was uncertain.

The following variables were collected and studied: age, gender, location, recurrence, comorbidities (hypertension, ischemic heart disease, chronic obstructive pulmonary disease, chronic renal failure, diabetes, dyslipidemia, obesity, surgery a month before the event, neoplasm), clinical symptoms and signs (abdominal pain, diarrhea, low digestive haemorrhage and abdomen), diagnostic method, treatment (medical, surgery and surgical techniques), chronic medication potentially implied in IC, and in-hospital mortality due to IC. The laboratory variables studied included blood analysis with a complete blood count, ph, lactate, urea, creatinine.

The location of IC was divided into right colon (cecum to splenic flexure) left colon (splenic flexure to rectum) and pancolitis (all colon).

### Statistical analysis

The data was tabulated in a computerized spreadsheet (Office Excel 2016®). The statistical analysis was carried out using the IBM SPSS Statistics program, Version 22.0. The objective of this study was to identify predictive factors related to in-hospital mortality due to IC. In the case of quantitative variables with normal distribution, the mean and the standard deviation were studied. The median and the interquartile range were determined in variables that did not adjust to normal. In the categorical variables, the frequency distribution was determined.

Univariate analysis using chi-square or Fisher’s exact test and Student t or Mann-Whitney’s U test were performed to assess the association between patient’s characteristics and mortality. Variables with an independent influence on mortality were identified by stepwise binominal multiple regression analysis. The decrease was considered a dependent variable. Odds Ratio (OR) and 95% confidence intervals were used to quantify the effect of each variable. Statistical significance was set at  $p < 0.05$ .

**Results**

Nine hundred twenty seven cases were initially considered, however, only 286 patients fulfilled the diagnostic criteria of IC and were included in this study. The mean age was  $76 \pm 11$  years (range: 28 - 101 years); 173 patients (60.5%) were female and 113 (39.5%) men ( $p < 0.01$ ). Age distribution showed: 25 (8.7%) were less than 60 years old, 44 (15.4%) 60 - 69 years old, 84 (29.4%) 70 - 79 years old, and 133 (46.5%) 80 years old or more ( $p < 0.001$ ).

A total of 266 patients (93%) presented only one episode of IC, 19 patients (6.6%) two episodes and one patient (0.3%) three episodes. In addition, 9 patients (3.1%) had suffered from an episode of IC previous to the years studied (1988 - 2015) (not included in this analysis).

Comorbidities of the patients included: hypertension (63.6%,  $n = 182$ ), dyslypemia (30%,  $n = 86$ ), diabetes (27.3%,  $n = 78$ ), ischaemic heart disease (26.2%,  $n = 75$ ), chronic obstructive pulmonary disease (14.4%,  $n = 41$ ), episode of hypotension in the previous days (9.8%,  $n = 28$ ), chronic renal failure (7.3%,  $n = 21$ ). In 15 patients (5.2%) a history of surgical procedure in the previous month was recorded (abdominal aortic aneurysm open repair ( $n = 8$ , 53.3%), colorectal surgery ( $n = 4$ , 26.6%), hip surgery ( $n = 2$ , 13.3) and pulmonary resection surgery ( $n = 1$ , 6.6%). Morbid obesity was present in 12 patients (4.2%).

CT with intravenous enhanced contrast was the first exploration technique performed in patients admitted for abdominal pain. A colonoscopy was performed to patients who referred lower rectal bleeding. CT was performed in 178 cases (62.2%) and provided unequivocally compatible signs with IC in 151 patients whereas in 47 cases a colonoscopy was necessary. The diagnosis was based on the findings of colonoscopy in only 58 other patients. In 30 additional patients the diagnosis of HF was made after studying the surgical specimens.

In 232 (81%) patients the predominant symptom was abdominal pain (Table 1). This was mild-moderate in 135 patients (47.2%), and in 97 (33.9%) it was acute and severe and without rectal bleeding, with signs of peritoneal irritation and severe general affectation. Lower digestive hemorrhage was present in 153 (53.5%) and 77 (26.9%) had non-bloody diarrhea.

	Left Colon (n = 210)	Right Colon (n = 39)	Pancolitis (Left + Right Colon) (n = 37)	p value
<b>Abdominal Pain</b>				
Mild-localized (n = 135)	120 (56.6%)	9 (23%)	6 (16.2%)	0.032
Acute Abdomen (n = 97)	42 (20%)	27 (69.2%)	28 (76.6%)	0.001
Non-Bloody Diarrhea (n = 77)	63 (30%)	6 (15.4%)	8 (21.6%)	0.088
Lower Intestinal Bleeding (n = 153)	134 (63.8%)	8 (20.5%)	11 (29.7%)	0.001
Rectorrhagia Solo (n = 27)	24 (11.4%)	2 (5.1%)	1 (2.7%)	0.266
Abdominal Pain (n = 95)	48 (22.9%)	27 (69.2%)	20 (54%)	0.001

**Table 1:** Clinical symptoms according ischemic colitis location.

Most of patients presented only left colon involvement (73%, n = 210), 39 (13.6%) had right colon involvement, and 37 (12.9%) had right and left colon affected (pancolitis). We analyzed the relationship between the clinical and the segment of the colon affected (Table 1). IC localized in left colon presented more frequently as mild-moderate abdominal pain (120 cases; 56.6%) (p = 0.032), and with lower intestinal bleeding (134 cases; 63.8%) (p = 0.001). Clinical presentation as severe pain and acute abdomen were highly frequent localized in right colon (27 patients; 69.2%) and in patients with pancolitis (28 patients; 76.6%). However it was significantly less frequent in cases localized in left colon (42 cases; 20%) (p = 0.001).

Abdominal pain was the only clinical feature present in 27 (69.2%) cases of IC localized in the right colon, and in 20 (54%) cases with pancolitis. However, it was present in only 48 (22.9%) cases of left colon (p = 0.001).

Only 96 patients (33.6%) underwent emergency surgery whereas in 190 patients was not necessary. When surgery was required the following techniques were used: segmental colectomy with stoma (41.6%, n = 40), total colectomy and ileostomy (32.2%, n = 31), segmental colectomy with anastomosis (20.8%, n = 20), total colectomy with anastomosis (3.1%, n = 3) and only exploratory laparotomy without any resection (2%, n = 2).

Death occurred in 50 patients (17.5%), 28 (29.1%) among those that underwent surgery and in 22 (11.5%) that received conservative treatment (p = 0.001).

Extent of IC was associated with adverse outcome. Death occurred in 15 (38.4%) patients with involvement of the right colon and in 14 (35.9%) with involvement of the entire colon. However, 21 patients died with involvement of the left colon (10%) (p = 0.001).

The type of symptoms presented by the patient was associated with outcome. Among those 232 patients admitted for abdominal pain died 49 (21.1%), while we observed a single (1.8%) death among those without abdominal pain (p = 0.001). Among the 153 patients who consulted for rectorrhagia detected 13 (8.5%), while among the 133 patients who did not have a relative recorded 37 (27.8%) (p = 0.001). In 28 patients (9.7%) a previous episode of hypotension was recorded in the previous week, among them 10 (35.5%) (p = 0.012).

Laboratory data included in the analysis did not show relationship with disease outcome.

According to the multivariant analysis, the presence of abdominal pain was the main predictive factor. We detected that those patients with abdominal pain had a higher risk of death (17,3 times, 95% CI: 2.25 - 142,38). The localization and the presence of bleeding are also predictive value independent. The involvement of the right colon and pancolitis presented a risk of dying 2,3 (95% CI: 1.065 - 4.85) times higher than the involvement of the left colon. The presence of bleeding behaves as a protective factor, associated with a decrease in the risk of death of 0.4 (95% CI: 0.201 - 0.890) times.

	Patients	Deceased	p value	Odds Ratio	CI 95%
<b>Gender</b>					
Men	113	22 (19.4%)		1	
Women	173	28 (11.1%)	0.288	0.79	0.45 - 1.48
<b>Age (years)</b>					
< 60	25	5 (20%)		1	
69 - 69	44	11 (25%)		1.08	0.37 - 3.15
70 - 79	84	9 (10.7%)		1.44	0.64 - 3.23
>= 80	133	25 (18.8%)	0.198	0.51	0.22 - 1.17
<b>Location of IC</b>					
Left Colon	210	21 (10%)		1	
Right Colon	39	15 (38.4%)		13.5	2.13 - 85.4
Pancolitis	37	14 (35.9%)	0.001	4.9	2.45 - 12.2
<b>Abdominal Pain</b>					
No	54	1 (1.8%)		1	
Mild-localized	135	12 (8.8%)	0.001	32.06	4.251 - 241.8
Severe-Diffuse	97	37 (38.1%)	0.125	5.03	0.638 - 39.7

<b>Non-bloody diarrhea</b>						
Yes	77	8 (10.3%)		1		
No	209	42 (20%)	0.078	2,16	0.96 - 4.85	
<b>Rectorrhagia</b>						
No	133	37 (27.8%)		1		
Yes	153	13 (8.5%)	0.001	0.24	0.12 - 0.47	
<b>Management</b>						
Non-Surgical	190	22 (11.5%)		1		
Surgical	96	28 (29.1%)	0.001	4.38	1.68 - 5.87	
<b>Hypertension Arterial</b>						
No	104	17 (16.3%)		1		
Yes	182	33 (18%)	0.416	1.13	0.55 - 2.1	
<b>Ischemic cardiopathy</b>						
No	211	35 (16.5%)		1		
Yes	75	15 (20%)	0.307	1.25	0.64 - 2.46	
<b>COPD</b>						
No	245	45 (18.3%)		1		
Yes	41	5 (12%)	0.23	0,67	0.22-1.66	
<b>Cronic Renal Failure</b>						
No	265	44 (16.6%)		1		
Yes	21	6 (28.5%)	0.138	2	0.74 - 5.46	
<b>Arterial Hypotension episodic recently</b>						
No	258	40 (15.5%)	0.012	1	1.3 - 7.03	
Yes	28	10 (35.5%)		3.08		
<b>Diabetes</b>						
No	208	35 (16.8%)		1		
Yes	78	15 (19%)	0.376	1.17	0.6 - 2.3	
<b>Obesity</b>						
No	274	48 (17.5%)		1		
Yes	12	2 (16%)	0.65	0.94	0.2 - 4.43	
<b>Leukocytosis</b>						
< 12.000	135	28 (20.7%)		1		
> 12.000	130	19 (14.6%)	0.126	0.65	0.34-1.24	
<b>Hemoglobin</b>						
>10	234	41 (17.5%)		1		
< 10	28	6 (21.4%)	0.386	1.28	0.49 - 3.36	

**Table 2:** Risk factors of death due to ischemic colitis. Univariant analysis.

	Odds Ratio	95% IC	p value
Gender (Men)	0.896	0.443 - 1,180	0.759
Age	1.006	0.975 - 1.039	0.689
Right colon or pancolitis	2.273	1.065 - 4.850	0.034
<b>Abdominal Pain</b>			
Mild-Located	17,898	2,250 - 142,379	0.006
Severe-Diffuse	4,650	0,583 - 37,092	0,147
Lower Intestinal Bleeding	0.423	0.201 - 0.890	0.023

**Table 3:** Multivariate analysis of risk factors of deceased.

### Discussion

Ischemic colitis occurs when there is an acute, transitory impairment in blood flow of the colon, below that required for the metabolic needs [8]. Blood flow need not stop, but reduce significantly to cause ischemic damage. Ischemic colitis and mesenteric ischemia are different disorders and are often confused. IC is caused by the succession of ischemia and the reperfusion injury due to relay of inflammatory molecules. This leads to mucosal ulceration, inflammation, and hemorrhage. The duration and severity of hypoperfusion determines whether the colonic injury is transitory, with progression to repair, or definitive, with evolution irreversible and necrosis [3].

The data obtained indicate that the IC has an elevated morbidity and mortality. In our study 96 (33.6%) cases needed surgery and 50 patients died (17.5%). Mortality has occurred within a range of previously reported rates for patients with IC who need hospitalization (4 - 20%) [4,11-14]. However, this group is not significant, so represents this patients with severe IC and not all cases need hospitalization. Surgical rates in literature range between 5.7 - 45% of hospitalized patients [4,13,15]. The reason for this and double mortality is due to intestinal ischemia and the high basic comorbidity usually found in these patients. Our data shown that none comorbidity, individually, demonstrate significant relation with mortality, but accumulation of them rather than one of them specifically, is more important for outcome.

We have verified that no specific cause for ischemia is identified in most cases, and such episodes may hypothetically be given to localized non-occlusive ischemia, likely to result from small-vessel disease [3]. On the other hand, in a minority of cases the aetiology is identified and most commonly follows an episode of systemic hypotension, decreased cardiac output, or surgery. In our series, in 28 patients (9.8%) an episode of hypotension was recorded in the previous days (9.8%, n = 28), and in other 15 patients (5.2%) a history of surgical procedure in the previous month was recorded (abdominal aortic aneurysm repair in 8, colorectal surgery in 4, hip surgery in 2 and pulmonary resection in one).

Mortality was higher among patients who received surgical management than among those who received medical support treatment. Death occurred in 28 (29.1%) among those underwent surgery and in 22 (11.5%) that received conservative management (p = 0.001). The indications for surgery included the development of peritonitis, hemodynamic instability, and intractable disease. The increased death rate of patients who underwent surgery reflects the severity of the disease once an irreversible intestinal ischemia has been established.

In our study the demographics characteristics of the patients were similar to previous reports. We have confirmed that IC can appear at any age [3]. However, neither gender nor age were associated with a higher frequency of death, and both factors, were not associated with an increased risk of death in the multivariate analysis.

The data obtained indicated that the location of the IC and the clinical presentation are related. The cases located in the sigma were more frequently manifested by rectorrhagia whereas the cases with right colon involvement manifested more frequently abdominal pain or acute abdomen. In addition, we have confirmed that the clinical presentation of IC shows a close relationship with evolution and mortality. Those patients whose main presentation is abdominal pain had worse evolution. Among those 232 patients admitted for abdominal pain died 49 (21.1%), while a single (1.8%) patient died among the 54 who did not present with abdominal pain ( $p = 0.001$ ). In the multivariate analysis, the presence of abdominal pain increased by 17,9 times the risk of death (95% CI: 2,250 - 142,379). On the other hand, the presentation as lower intestinal bleeding was associated with lower mortality. Of the total of 50 patients who died, 13 patients (26 %) presented intestinal bleeding ( $p = 0.001$ ). In the multivariate analysis, this data behaved as a protective factor, associated with a lower risk of death (OR: 0.4, 95% CI: 0.201 - 0.890). Most episodes of rectal bleeding were autolimited and only a minority of cases were severe. The lack of gastrointestinal bleeding has been identified as a risk factor for death in previous publications [3,13,16,17]. Previous studies have found that the absence of rectal bleeding is a protective risk factor for surgery, delayed operation and death [6,16]. Likewise, the presence of rectal bleeding was protective and conferred better outcome per Longstreth and Yao [18]. Patients with pain progress more frequently to the irreversible form of HF with necrosis and intestinal gangrene, on the contrary the presentation of lower intestinal bleeding, as a main sign, seems a more benign and reversible form of the clinical picture.

The results obtained indicate that there are differences in the presentation and evolution of IC depending on the affected colon segment. We observed that left colon involvement is more frequent and associated with lower mortality. On the other hand, the involvement of the right colon or the entire colon is associated with higher mortality (OD: 2,3, 95% CI: 1,065 - 4,850) than the exclusive involvement of the left colon.

Location and extension of ischemia have previously been identified as predictors of postoperative mortality [7,11]. A study by Genstorfer, *et al.* [17] found 3.8 and 11 times OR for death in right-sided colitis and pan colitis compared with left side, respectively. Longstreth and Yao [18] found at 14.6 times OR for death in right-sided and bilateral colitis when compared with left-sided colitis. The segmental nature of IC can be explained by the vascular anatomy of the colon and rectum. Colonic blood flow is supplied by three vessels: the superior mesenteric artery (SMA), IMA, and superior hemorrhoidal artery [3]. There are areas of the colon which are particularly susceptible to ischemic as a result of their location between two different supplies. These regions include the splenic flexure (Griffith's point) and sigmoid colon (Sudeck's point) which are the points of connection between the three arterial systems and are the critical points of ischemia. The segmental nature of IC has been known for decades. However clinical presentation and prognosis is more favourable in the left side. Collateral circulation in the sigmoid colon is more efficient and this contributes to a more frequent episode of IC being transient and reversible. When pancolonic or right involvement are observed, there are probably hypoperfusion in both the SMA and IMA circulations [10].

Our study has several limitations. Data were obtained retrospectively, which may have affected the results because of the drawbacks of such an investigation. However it is obvious that there are many possible clinical forecast factors that have not been included and analyzed. It would have been very interesting to have included more analytical data such as lactate levels, PCR, or procalcitonin, we could not do it because they had not been determined in a significant number of patients.

## Conclusion

The IC is a disease associated with a high mortality. This is due to the severity of the intestinal ischemia and to the coexistence of these patients of a severe comorbidity. Symptoms and the location of the affected intestinal segment allows to differentiate two clinical forms with different prognosis. Patients with exclusive involvement of the left colon and with intestinal bleeding clinic have a better and reversible form of HF. Patients with mainly abdominal pain and involvement of the right colon or pancolitis involve more frequently to the irreversible form of HF with necrosis and intestinal gangrene.

### Conflict of Interest

There are no conflicts of interest.

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