



The Predictors of Poor Outcomes of Ischemic Colitis, Including the Severity of Histopathological Features: A Four-Year Chart Review of 74 Consecutive Cases

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Abstract

Purpose Ischemic Colitis (IC) can be transient or it can have evolving presentations that have a profound impact on outcome. Based on a chart review of cases, the aim of the study was to characterize the prevailing histological features of IC and to determine to what extent the severity of necrosis affected outcomes.

Methods: We conducted a retrospective study of patients with IC who were referred to our department of surgery from 2013 to 2016. Moreover, the relationships among IC presentations, comorbidities and surgical procedures were surveyed. The severity of necrosis was investigated as the main histological feature, and a morphological criterion was used to grade necrosis from mild to severe differences between groups were determined with a univariate analysis, variables predicting death with a multivariate analysis and a flow-chart identifying clinical behavior.

Results: Among 82 patients with an IC diagnosis, 74 (90.3%) were referred for surgical consultation, and 8 (9.7%) patients were not because they had fulminant IC. Comorbidities affected 53 (71.6%) patients. Ten (13.5%) patients underwent surgery, all of whom had severe necrosis, and 6 (60%) died perioperatively. The severity of necrosis impacted whether surgery was performed for evolving forms of IC (OR: 9.4, 95% CI: 1.8-48.8, p=0.002), the number of patients who had died by follow-up (OR: 0.2, 95% CI: 0.08 to 0.7, p=0.013), and the frequency of right-sided IC (χ -square 12.4, p=0.029); however, necrosis severity was not affected by the presence of comorbidities (OR: 2.2, 95% CI: 0.724 to 7.124, p=0.154). Advanced age (OR: 1.119, 95% CI 1.015 to 1.234, P=0.023) and need of surgery predicted death (OR: 5.597, 95% CI 1.125 to 27.842, P=0.035). Conclusion: This study quantified to what extent the severity of histological findings affected poor outcomes and what factors predicted death. These findings allowed us to suggest prophylactic therapies for transient form of IC.

Keywords: Ischemic colitis; Ischemic colitis pathology; Factors predicting death; Urgent colorectal surgery

Introduction

Ischemic Colitis (IC) has a wide spectrum of presentations characterized by an acute abdomen event; particularly affected by IC are elderly patients, most of whom have comorbidities. The clinical impact of IC depends on the extent of the disease and the site of onset. In addition, due to the presence of non-specific abdominal symptoms, endoscopic investigations may be carried out using biopsies of random sections in the absence of lesions suggestive of IC (e.g., suspicion of microscopic colitis). Nevertheless, the related biopsies may unexpectedly highlight a histology compatible with IC, and the distribution of IC varies among the segments of the colon, with multifocal locations. This evidence does not correlate with the clinical picture, and we are very likely to encounter transient forms detected by histological analysis that favor the clinical evolution of IC. It is worth

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noting that IC presentation differs in relation to the cause (occlusive or non-occlusive, arterial or venous), severity of symptoms at onset, location (right, left, or rectum), extension (multifocal, segmental, or isolated) and spectrum of histopathological damage (sub-epithelial, hemorrhagic and edematous). The following classification has been proposed recently and summarizes the described aspects: Reversible IC, transient, chronic ulcerative, ischemic colonic stenosis, gangrene colic and fulminant pan colitis [1]. Moreover, IC is one of three clinical manifestations of intestinal ischemia, along with acute and chronic mesenteric ischemia [2]. Regarding IC, the literature studies that evaluate its natural history are rather fragmented and relatively recent. In fact, IC has been described for fifty years, but only since 1992 has IC been the subject of comprehensive studies [3,4]. In our series, it was notable that we detected the clinical presentations attributable to IC, either transient or evolving, with the aim of investigating whether the different histological aspects that emerged might have influenced outcomes. Furthermore, we examined the relationship between clinical course, extension, prevailing location, associated comorbidities and histological necrosis severity. The outcome assessment involved an important clinical implication because it quantifies a percentage estimate of transient forms of IC compared to evolving forms, allowing us to approximate a negative predictive value of the examined variables depending on the clinical picture. Finally, we established to what extent the severity of the necrosis impacts mortality. To this end, we created a flow-chart of our clinical approach that may indicate the most suitable timing for dealing with each case.

Materials and Methods

Patients

We first examined all histological and intraoperative findings, including biopsies and samples, related to the diagnosis of IC (e.g., necrosis and intestinal infarction) in patients admitted to or operated on in the general surgery unit or referred to the digestive endoscopy service of Mantua Hospital over a period of 4 years. Patients were identified using computerized search codes of ICD-9 (International Classification of Diseases, ninth revision) for colon ischemia. The data collected were uploaded to the official database of our health institution (Microsoft Excel, Redmond WA, USA).

Baseline data documenting

The analysis of the workup was carried out first by analyzing the main symptoms and then investigating the relation between the onset of the symptoms and diet. The diagnosis was performed through endoscopy, radiological imaging and intraoperative findings. Five major groups were identified based on the IC location. Therefore, the colon was divided into the cecum, ascending colon and hepatic flexure (segment 1), transverse colon (segment 2), splenic flexure and descending colon (segment 3), colon sigma (segment 4), and rectum (segment 5). By convention, the term "segmental IC" was attributed to the localization of IC in a single segment (SIC), while DSIC indicated a double segment IC, whether contiguous or not, and finally Widespread IC (WIC) was the presence of multiple segment involvement (three or more), albeit with different degrees of extension. With reference to patients' characteristics, the factors related to disease and the type and frequency of comorbidities were considered. Transient or evolving forms of IC were used to characterize the clinical course. The former cases were always diagnosed by endoscopic biopsy, while the latter were diagnosed by histology following resection surgery. Since the histological diagnosis was in some cases unexpected, we reviewed all

the case descriptions and quantified the number of cases in which the endoscopic features were not suggestive of IC. According to a comprehensive review the endoscopic appearance of the transient ischemic colitis consisted of petechial hemorrhages, edematous and fragile mucosa, segmental erythema, scattered erosion, longitudinal ulcerations, and sharply defined segment of involvement [5]. For the definition of all the histological patterns, we took into account a very recent study whose objective was to correlate the various aspects of IC with symptoms and their duration [6]. According to the study, we focused only on the presence of necrosis among all histological findings because this is the main sensitive, a priori, data. Patients with right IC location and poor outcomes are more likely to exhibit necrosis. Further, the severity of necrosis was classified as mild (non-gangrenous) or severe (gangrenous), taking into account the histological features described in young women with reversible IC [7]. By convention, in cases undergoing simple biopsy, the IC was classified as mild if the presence of ischemic alterations was limited to the mucosa and submucosa; these features show damaged structural architecture inside the mucosa but the fundamental constituents (crypts, chorion and muscularis mucosa) are preserved. IC was as classified as slight necrosis when necrotic aspects are detected, but they were contiguous to damaged but intact mucosa. Severe IC was defined in the biopsy specimen whenever completely necrotic fragments with no recognizable constitutive mucosal were found. On full-thickness specimens of surgical patients, the IC was defined as severe if transmural necrosis showed involvement of the muscular tunic. These aspects were considered part of the framework of transmural intestinal infarction. Moreover, we included neoplastic-like IC whenever particularly ulcerated areas and edematous inflammatory infiltrates were present and were accompanied by vascular congestion, simulating an occlusive neoplasm [8]. These findings parallel the "thumbprints" or "pseudo-tumors" found in barium studies [9]. Finally, we observed cases of massive intestinal infarction (fulminant IC) in which either computed tomography or exploratory laparotomy had been carried out. These cases were not suitable for follow-up; therefore, only the overall incidence was assessed.

Follow-up

The deadline of follow-up was set for December 31st, 2018, and follow-up was conducted at 6-month intervals with telephone survey by the attending general practitioner who was asked to provide information on the individual patient's clinical condition and the likely date of death. During the follow-up, the therapies used in patients with transient evolution were described. In addition, both the perioperative and long-term mortality rates were calculated. The correlation between IC extension and comorbidity was also investigated along with the type of procedure performed. We verified both the outcomes of living subjects and those who died either in the perioperative period or in the following months/years, with the goal of establishing which deaths were attributed to IC and which were not. Furthermore, a univariate comparative analysis was used with the aim of identifying those variables that had been influenced by the severity of necrosis. Finally, those variables that predicted death were identified by a multivariable model using binary logistic regression. Among these factors, the age was differentiated in more advanced (75 years older) and less than 75 years old. The institutional review board ethical approval was required and obtained.

Statistical analysis

The relationship between gravity of necrosis with the other

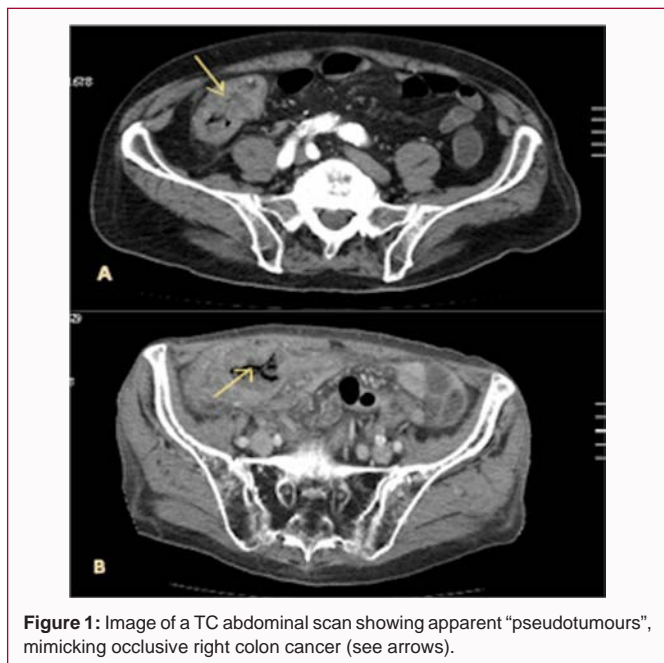


Figure 1: Image of a TC abdominal scan showing apparent "pseudotumours", mimicking occlusive right colon cancer (see arrows).

variables was evaluated using a chi-squared test. Odds ratio and 95% confidence intervals were used for categorical variables. To assess the impact of each variable with severe histology, a univariate analysis was performed. Factors that predicted death were identified by multivariable models using binary logistic regression by backward-stepwise selection with the removal testing based on the probability of the Wald statistic. The tests were two tailed, and p-values less than 0.05 were considered statistically significant. Analyses were performed using the Statistical Package for Social Sciences (SPSS) version 26.0 (IBM, Armonk, NY, USA).

Results

In the period between January 2013 and December 2016, 82 patients with IC were referred to the general surgery and gastroenterology units of the ASST of Mantua. Among these, 74 patients had follow-up assessments, representing 90.2% of the entire cohort. Eight (9.7%) subjects had massive intestinal infarction and accounted for 44.4% of all evolving forms ($n=18$ in total). Among these, 3 (3.6%) patients underwent explorative laparotomy, while 5 (6.1%) patients underwent CT investigation and did not undergo surgery due to irreversible septic shock. Excluding the subjects with massive intestinal infarction, the average age was 74.6 years ($SD \pm 8.526$), and there were 50 (67.6%) female and 24 (32.4%) males subjects. The prevalent symptoms were pain in 63 (85.1%) cases with non-specific features of a predominantly cramp-like pain and an average onset of 1 h after eating. Diarrhea and abdominal bloating were present in 41 (55.4%) cases, of which 23 (30.1%) cases showed mucus and blood in the stool. Both pain and diarrhea were detected in 42 (56.7%) cases.

A histological diagnosis of IC was made following endoscopic biopsy in 62 (83.8%) cases, and IC was diagnosed using radiological imaging in 2 (2.7%) cases; in the latter patients, IC was detected in the specimen collected during colic resection performed for a radiological-suspected neoplasia (Figure 1). In 15 (24.2%) patients who underwent biopsy, the endoscopic results were not suggestive of IC. Based on the extent of involvement of the colonic segments, 15 (20.3%) patients presented with WIC, 12 (16.2%) with DSIC

Table 1: Characteristics of the 74 patients in follow-up (from the 82 cases observed). ($n= \pm SD/(\%)$).

Mean age, years	74.6 \pm 8.5
Median	77
Range	48-92
Advanced Age (>75 yrs)	44 (59.4)
Males	24 (32.4)
Symptoms*	
Pain	63 (85.1)
Diarrhoea	41 (55.4)
Fever	13 (17.6)
Constipation	27 (36.5)
Diagnostic modality	
Endoscopy	62 (83.8)
Imaging	2 (2.7)
Surgery	10 (13.5)
Type of IC Extension	
Widespread (≥ 3 , WIC)	15 (20.3)
Double Segmental (2, DSIC)	12 (16.2)
Segmental (1, SIC)	47 (63.5)
Detected IC Locations*	
Right	18 (24.3)
Transverse	24 (32.4)
Left	39 (52.7)
Sigma	31 (41.9)
Rectum	21 (28.4)
Comorbidities	53 (71.6)
Patients operated on	10 (13.5)
Perioperative mortality (<30 days)	6 (8.1)
Mean follow up, months	27.7 \pm 14.2
Dead	12 (16.2)
Alive	56 (75.7)

*The association of multiple symptoms and IC locations makes the total number and percentages much higher than the overall cases.

and 47 (63.5%) with SIC. Comorbidities were present in 53 (71.6%) patients. Ten (13.5%) subjects underwent surgery, with perioperative mortality in 6 (8.1%) cases. The therapies adopted in the transient forms of IC depended on the type of comorbidity. For the distribution of comorbidities, in patients with fibrillating or ischemic heart disease, low-molecular weight heparin therapy was required, and the dosage was based on BMI (range 4000 U. to 6000 U). The heparin therapy lasted for 6 months for therapeutic prophylaxis and was also administered in 13 (18.9%) subjects with arterial hypertension; however, the therapy was not affected by concomitant cardiopathy in subjects with diabetes mellitus, chronic obstructive pulmonary disease and non-cardiac obesity. No treatment was administered in subjects with chronic renal failure. Table 1 shows the overall data regarding patient characteristics, comorbidities, presentation type and location and the number of deceased patients and causes of death. Table 2 lists in detail the comorbidities that were present in 71% of cases and their distribution. Table 3 shows the relationship between the number of affected colonic segments and the relative rates along with comorbidities. Figure 2 shows the distribution by

Table 2: Types of Comorbidities [in 53 (71.7%) patients].

Disease	n= / (%)
Chronic cardiac failure	35 (47.3)
Chronic cardiac ischemia	15 (20.3)
Chronic fibrillation	20 (27.0)
Arterial Hypertension	48 (64.9)
Diabetes mellitus	13 (18.9)
COPD*	5 (6.75)
Chronic renal failure	7 (9.45)
Obesity (>28 BMI [†])	2 (2.7)

*COPD: Chronic Obstructive Pulmonary Disease; [†]BMI: Body Mass Index

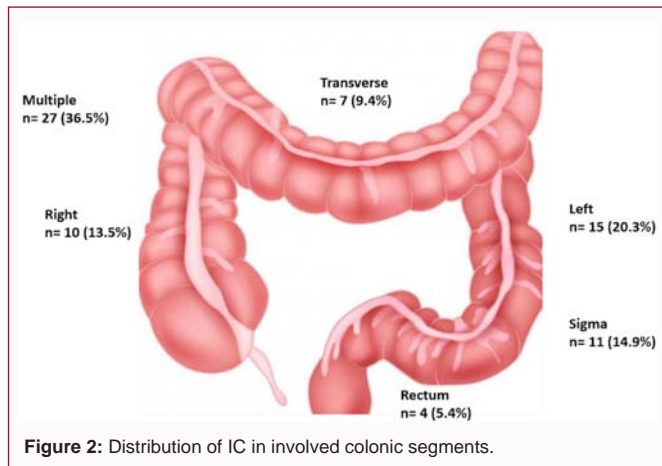


Figure 2: Distribution of IC in involved colonic segments.

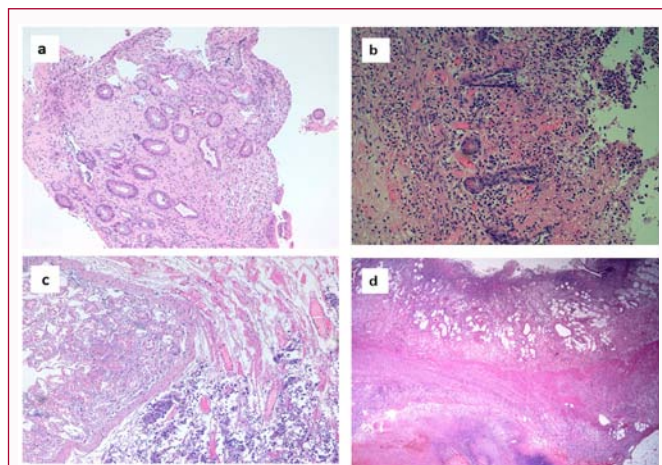


Figure 3: a, b, c, d Histological features of IC in both biopsies and resected specimens.

a. Early mild reversible ischemic colitis on biopsy: This photograph was taken in a patient biopsied two weeks after the onset of symptoms. In addition to superficial erosion and mucin depletion, note the extensive lamina propria fibrosis, and minimal focal cryptitis; E&E 100x.
 b. Reversible but severe ischemic colitis associated with right colon infarction: In addition to the superficial erosion and severe mucin depletion in withered crypts, note the neutrophilic cryptitis possibly related to deferred intervention. E&E 200x.
 c. Severe ischemic colitis on right hemicolectomy. Note the coagulative necrosis of mucosa with pathognomonic "ghost cells" in crypts and gangrenous necrosis of submucosa (and muscular tunic); E&E 100x.
 d. Severe ischemic colitis on left hemicolectomy: Note the transmural colic infarction with gangrenous necrosis; E&E 40x.

site of IC in decreasing order of frequency. Ten (13.5%) subjects underwent surgery. Table 4 shows the types of surgery, which

Table 3: Relationship between distribution of IC extension and comorbidities (53 patients).

	All	WIC ¹	DSIC ²	SIC ³
	n= / (%)	n= / (%)	n= / (%)	n= / (%)
Heart disease	35 (66.0)	10 (18.9)	5 (9.5)	20 (37.7)
Chronic cardiac ischemia	15 (28.3)	4 (7.5)	2 (3.8)	9 (17.0)
Chronic fibrillation	20 (37.7)	6 (11.4)	3 (5.7)	11 (20.7)
Arterial Hypertension	48 (90.6)	10 (18.9)	8 (15.1)	30 (56.6)
Diabetes mellitus	13 (24.5)	0 (0)	0 (0)	13 (24.5)
COPD*	5 (9.5)	2 (3.8)	0 (0)	3 (5.7)
Chronic renal failure	7 (13.3)	2 (3.8)	2 (3.8)	3 (5.7)
Obesity (>28 BMI)	2 (3.8)	0 (0)	0 (0)	2 (3.8)
No comorbidities	21 (39.7)	3 (5.7)	5 (9.5)	13 (24.5)

WIC¹: Widespread IC; DSIC²: Double Segmental IC; SIC³: Segmental IC; *COPD: Chronic Obstructive Pulmonary Disease

Table 4: Number of types of procedures carried out in patients, depending on the extension of the involved segments.

Procedure	WIC ¹	DSIC ²	SIC ³
Right colectomy	0	1	5
Left colectomy	0	0	2
Segmental resection [†]	0	0	1
Other ^{**}	0	0	1

WIC¹: Widespread Ischemic Colitis (3 or more than affected segments); DSIC²: Double Segmental Ischemic Colitis; SIC³: Segmental Ischemic colitis; [†]Anterior Rectal Resection; ^{**}Right Colostomy

depended on the number of affected segments. All histological specimens of the evolving forms in patients who underwent surgery (10 cases) showed IC with severe necrosis, while in the non-surgical patients, the biopsies revealed slight necrosis in 45 (60.8%) cases and severe necrosis in 19 (25.7%) cases. Figure 3 illustrates the histological features of both slight and severe colitis (a-d), including the main details that were found, specifying whether the samples were biopsy or resected specimens. The average follow-up was 27.7 months (SD ± 14.1). The number of living subjects at the end of follow-up was 56 (75.7%). Among these subjects, 3 patients were advised to repeat endoscopy due to a mild recurrence of symptoms suggestive of new onset IC. These patients complained of pain and diarrhea after an average time of 15 months. All endoscopic investigations still showed the presence of IC in a single segment with slight necrosis, but for these patients, the clinical situation was transient. For the 18 (24.3%) patients who died, perioperative death occurred in 6 (8.1%), despite Intensive Care Unit (ICU) hospitalization, and the causes were complications of pre-existing cardio-vascular comorbidities leading to multiple organ failure. The remaining 12 (16.2%) patients died in the follow-up period due to comorbidity-related causes.

Outcomes

At univariate analysis, the variables significantly associated with the severity of necrosis were as follows: Surgery as a diagnostic modality (OR: 9.474, 95% CI: 1.838 to 48.821, p=0.002), patient death at follow-up (OR: 0.255, 95% CI: 0.084 to 0.773, p=0.013), and multiple locations of IC (χ-square 12.439, p=0.029). The presence of comorbidities was not associated with severe necrosis (OR: 2.2, 95% CI: 0.724 to 7.124, p=0.154) (Table 5). At multivariate analysis advanced age (OR: 1.119, 95% CI: 1.015 to 1.234, P=0.023) and the need of surgery (OR: 5.597, 95% CI: 1.125 to 27.842, P=0.035) predicted death (Table 6). The difference of incidence between the

Table 5: Univariate analysis, comparing gravity of necrosis with variables.

Variable	Mild n= (%)	Severe n= (%)	OR	95 % CI	Chi square	p
Gender						
Male	15 (62.5)	9 (37.5)	0.938	0.342-2.569	0.016	0.900
Females	32 (64.0)	18 (36.0)				
Diagnostic mode						
Endoscopy	45 (70.3)	19 (29.7)	9.474	1.838-48.821	9.447	0.002
Surgery	2 (20.0)	8 (80.0)				
Comorbidities						
Yes	16 (76.2)	5 (23.8)	2,271	0.724–7.124	2.033	0.154
No	31 (58.5)	22 (41.5)				
IC Location						
Right	4 (40.0)	6 (60.0)				
Transverse	7 (100.0)	0 (0.0)	12.439			0.029
Left	6 (40.0)	9 (60.0)				
Sigma	9 (81.8)	2 (18.2)				
Rectum	2 (50.0)	2 (50.0)				
Multiple	19 (70.4)	8 (29.6)				
IC Extension						
WIC	8 (53.3)	7 (46.7)	4.881			0.09
DSIC	11 (91.7)	1 (8.3)				
SIC	28 (62.2)	17 (37.8)				
Follow-up						
Dead	7 (38.9)	11 (61.1)	0.255	0.084–0.773	6.224	0.013
Alive	40 (71.4)	16 (28.6)				

WIC: Widespread Ischemic colitis; DSIC: Double Segmental Ischemic Colitis; SIC: Segmental Ischemic colitis

Table 6: Final model of binary regression analysis. Covariates included in the model were age, surgery, severe histology, hypertension, kidney insufficiency, and comorbidity class. More advanced age (>75 Yrs) n=44, 59.4% and surgery predicted death. Hypertension even though with P>0.05 was included in the model.

Covariates	B	P value	OR (95% CI)
Age	0.113	0.023	1.119 (1.015-1.234)
Surgery	1.722	0.035	5.597 (1.125-27.842)
Constant	-11.529		

while others evolve, but our observation aligns with important epidemiological studies where the mild (non-gangrenous) form of IC was transient in 80% to 85% of cases and the reversible was transient in approximately 50% of cases [10]. In view of a predictive estimate of the transient forms, the assessment of symptoms and the role of associated comorbidities could have been the first tool available to identify a fairly common profile of the majority of patients with IC. We have instead observed that the resulting symptoms were non-specific overall; they lasted for some weeks, irrespective of different IC presentations and ranged from moderate-to-severe colic or constant and poorly localized pain. According to the Carlson’s editorial, IC appears to be a spectrum of illnesses rather than a single entity, which makes the cause of the IC unknown in a non-negligible percentage of cases. The Author does not deal with cases in which IC appears to be caused by interruption of blood flow. Furthermore, he strongly suggests the extent of acute idiopathic IC, until proven otherwise [11]. A retrospective analysis of 400 cases with IC showed that: 94% of the subjects were not hospitalized but underwent a consultation [12]. In our series, the problem of following patients with transient IC over time and introducing precautionary treatment was dutifully noted. Treatment with low molecular weight heparin was precautionary used, with the exception of cases in which anticoagulant therapy had already been administered. This approach is in line with some authors who reaffirm the benefit of heparin therapy at least in the acute postoperative phase [13,14]. Additionally, anticoagulant therapy following discharge has also been proposed [15]. For this reason, due to lack of guidelines, some authors emphasize the urgency of planning prospective studies [16]. The patterns of IC, based on biopsy sampling, were determined retrospectively in a study covering 313 cases. In this subset of patients, comorbidities included hypertension in 78%, coronary disease in 39% and atrial fibrillation in 17% of cases [17]. The frequent association of comorbidities in elderly patients is responsible for hypotensive episodes that induce states of hemodynamic instability and affect the anatomical and physiological characteristics of the mesenteric circulation in the right colon with increased risk of IC evolving [18]. Finally, several large lists of predisposing factors for IC have been published. These studies also mention the role of recreational drug use in developing IC, including the effect of cocaine as illicit vasoconstrictor [19-21]. Interestingly, transient colonic ischemia represents a form of acute segmental colitis in young adults; before the 5th decade of life, spontaneous ischemic colitis is found almost exclusively in women and is associated with the clinical use of exogenous estrogenic agents [10]. For the prevailing locations of IC in relation to transient or evolving behavior, we also observed (Figure 2) that the left colonic side and the sigma were, for the most part, associated with transient forms, while for the right colonic side, several interventions were performed due to IC evolving. These data confirm that in the right colon, the occurrence is rare, but when IC does occur, it behaves as a more evolving form and presents a limited, mostly segmental extension [22,23]. It is

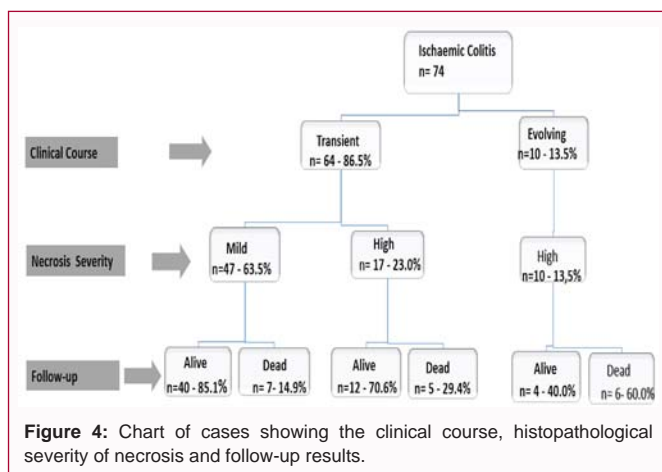


Figure 4: Chart of cases showing the clinical course, histopathological severity of necrosis and follow-up results.

mild necrosis of IC detected by biopsy (n=45) and the severe necrosis detected by surgery (n=10) was threefold as expected. By comparing the involvement of segments, we discovered that the incidence of IC in multiple segments was higher than that in single or double segments, with borderline significant difference (χ -square 4.881, p=0.09). The chart showing the clinical trends during the follow-up period, displays the distribution of living and deceased subjects depending on the severity of IC necrosis. A total of 85% of patients who showed mild necrosis on biopsy were still alive at follow-up, compared to 70% of those who showed severe necrosis. In detail, the presence of severe necrosis on biopsy accounted for a higher number of patients who died (n=5, out of 17: 29%), compared to the number of deaths in the presence of mild necrosis of which double (n=7, out of 47: 15%) (Figure 4).

Discussion

The results that we would have liked to find by analyzing literature data concerned what physiopathological patterns might have triggered a certain clinical IC behavior instead of another and why the IC presentations are transient in most cases. As expected, we were not able to explain why some cases of IC disappear quickly

worth noting that the occurrence of an evolving form of IC negatively affects prognosis. In fact, it is unlikely that major treatment advances will improve the prognosis favorably since many patients with IC are elderly [24]. The diagnostic modalities used in our series highlight the prevalence of biopsy carried out during colonoscopy compared to the histological diagnoses on the operative theatre. These data offer a starting point for the following considerations: We recall that the recent guidelines of the American College of Gastroenterology list the pathophysiological mechanisms, including that the damage from IC depends on a significant decrease in flow and not only on the interruption of blood flow. In addition, ischemia can be followed by damage from reperfusion, and the combined event can produce more major damage even for relatively short IC periods than that due to simple blood flow reduction without reperfusion [25]. On this aspect, much interest has been raised by studies on the dynamics of lesions over time, as it seems that the duration of structural modifications makes them reversible or likely to evolve within precise times (structural changes of the villi after 15 min, reversible mucosal sloughing after 3 h, and irreversible transmural necrosis and gangrene after 6 h) [26]. The results of the univariate analysis focused on the relationship between the severity of necrosis and the variables considered. Much to our surprise, the presence of comorbidities as a whole did not predict IC severity, and only borderline significance was shown depending on the wider extension of IC in multiple segments. Moreover, as for the presence of severe necrosis on biopsy, we may identify a worse outcome compared to the presence of mild necrosis. The major number of patients who died was only determined by comorbidities since IC never evolved, however, a negative prognostic role of severe necrosis may be also assumed if IC is detected on biopsies. Patients presenting clear clinical evolution in peritonitis underwent emergency surgical procedures. Epidemiologically, intervention was mandatory in up to 20% of cases because the clinical conditions deteriorated due to the development of hemorrhagic infarction [27]. IC can even occur in an isolated form, characterized by limited extension of the ischemic area; some studies have described this subgroup, focusing on the impact on outcome [28-32]. Our results align with the higher rate of mortality in patients who underwent surgery compared to those who did not. However, although this is a known and acquired evidence, we may identify some elements of novelty in this study because only few contributions have so far investigated the correlation between histological findings and clinical severity and outcomes, showing the most unfavorable outcomes in subjects who underwent colic resection, and who were then hospitalized in the ICU during the postoperative period [33]. According to the suggested classification and based on our results the histopathological features may be introduced as additional predictor of poor outcome for evaluating more comprehensively the IC clinical behavior [7]. Limitations the first limitation of the study is its retrospective design. The second is that the histological reports of biopsies in severe IC cases offer limited information, since only the mucosa is likely to be evaluated.

Conclusion

This chart review of cases allowed us, on the one hand, to show how IC behaved clinically; moreover, if transient forms of IC are diagnosed by biopsies, this result may be unexpected in a non-negligible percentage of cases. Consequently, a need arises to follow this cohort of patients over time and to suggest prophylactic lines of therapy. In addition, the statistical analysis can quantify how the severity of necrosis detected may affect outcome depending on the

variables considered. In fact, based on the flow-chart we may state that the endoscopic histology does not predict an evolution of IC while the severity of surgical histology might have an unfavorable predictive impact on outcomes. Finally, the prognostic relevance of our histological graduation needs to be confirmed by prospective, large-sized trials.

Declarations Related to Compliance with Ethical Standards

Authors contribution

Mantovani G contributed to the conceiving of the designing and the drafting of the manuscript. Colpani F managed histologic samples, critically classified and revised histologic slides, Manguso F, provided criticism and suggestion of high intellectual content, revised analysis of the manuscript. De Angelis M contributed to the conceiving of the designing and the drafting of the manuscript. Boccia L helped with the surgical procedures and the patients' management, revised the manuscript, Lucchini G contributed to the acquisition, analysis, interpretation of data for the work. Chiarioni G provided criticism and suggestion of high intellectual content, revised the manuscript. Palumbo A contributed to the conceiving of the designing and the drafting of the manuscript. Asteria CR ideated the study, analyzed the data, wrote the manuscript, all authors contributed equally to the manuscript and read and approved the final version of the manuscript.

Availability of data and material

Readily available for review if required.

Code availability

Statistical code available.

Ethical approval

We certify that the study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

The institutional "Valpadana Research Ethics Committee" has approved this observational study, after verifying that the country-specific requirements have been met according to the study design.

Consent to participate The Authors affirm that verbal informed consent was obtained from the medical practitioners who were phoned-interviewed to help us complete the follow-up of the patients enrolled in the study.

Consent for publication the authors affirm that human research participants provided informed consent for publication of the images in Figures 1, 3a, 3b, 3c and 3d. To this, additional related information was taken from the next of kin of the patients involved in the study.

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