Ischemic colitis

Incidence, Risk Factors, Clinical Manifestation and Outcome

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Thesis for the degree of Bachelor of Science
University of Iceland
Faculty of Medicine
School of Health Science

HÁSKÓLI ÍSLANDS

Ristilblóðþurrð

Nýgengi, áhættuþættir, sjúkdómsmynd og afdrif

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Supervisor: Einar Stefán Björnsson

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Prologue

The main supervisor was Einar Stefán Björnsson[1] and co-supervisors were Rodrigo Urðar Munoz Mitev[2], Jón Gunnlaugur Jónasson[2] and Páll Möller[3]

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Abstract

Ischemic colitis: Incidence, risk factors, clinical manifestation and outcome

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Introduction: Ischemic colitis (IC) is the most prevalent form of gastrointestinal ischemia and the second most common cause for lower gastrointestinal bleeding. The clinical course is diverse and the causes are many. Data on the incidence of IC in a population-based setting are largely lacking. The aims of this study were to determine the incidence, clinical manifestation and outcome of patients with IC, and to evaluate the prevalence of several risk factors for IC.

Material and method: A retrospective study was conducted on all patients, 18 years and older, who were admitted to the National University Hospital of Iceland and the Akureyri District Hospital with IC during a 5-year period from 2009 through 2013. A histological confirmation of IC was required for the diagnosis. Patients were identified by search for ICD-10 codes in the diagnosis database, for the term "ischemic colitis" in the text of electronic medical records and by search in database of the pathological department. Data were collected on age, gender, comorbidities, smoking habit, clinical presentation, treatment and outcome.

Results: A total of 89 patients fulfilled the predetermined criteria, 61 female (69%) and 28 males (31%). The overall mean age was 65 years (±16.7), for females it was 68 years (±14.1) but for males it was 59 years (±20.1) (p=0.0170). The mean incidence rate was 7.3 cases per 100.000 inhabitants per year. A total of 62 (70%) of patients had cardiovascular disease and 55 (62%) had a history of smoking habit. A total of 57 (64%) patients presented with abdominal pain, hematochezia and diarrhea. IC was localized in the left colon in 78 (88%) patients. Ten (11%) patients required surgery and/or died during hospitalization. Isolated right-sided colitis and simultaneous involvement of the right and left colon were predictive of poor outcome (p=0.0009 and p=0002). The 5 year recurrence rate was 9%. Hypertension and absence of abdominal tenderness were predictive of recurrence (p=0.0472 and p=0008). At the end of follow-up, 13 (15%) patients had died, 5 (6%) died from IC but 8 (9%) had alternative causes of death. Mortality rate for those who underwent surgery, 5/8 (63%), was higher than for those who did not, 8/81 (10%) (p=0.0014).

Conclusion: The mean incidence of IC was 7.3 cases per 100.000 inhabitants per year. Patients with ischemia confined to the right colon or located in both the left and right colon have worse prognosis. Patients diagnosed with hypertension and who present with no abdominal tenderness are more likely to experience recurrent IC. The high prevalence of smoking habit among patients with ischemic colitis warrants further research.

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Abbreviations

AF	Atrial Fibrillation
COPD	Chronic Obstructive Pulmonary Disease
CVD	Cerebrovascular Disease
HF	Heart Failure
HT	Hypertension
ICD-10	International Classification of Diseases, 10th Revision
IHD	Ischemic Heart Disease
IMA	Inferior Mesenteric Artery
INR	International Normalized Ratio
PAD	Peripheral Arterial Disease
PT	Prothrombin Time
SMA	Superior Mesenteric Artery
SNOMED	Systematized Nomenclature of Human Medicine

1 Introduction

Ischemic colitis, also known as colon ischemia, was first described by Boley et al. (1) and Marston et al. (2) in the nineteen-sixties. Since then, it has become a well-recognized clinical condition with characteristic histological findings (3). The incidence has been steadily increasing over the past decades and the disorder is now considered to be the most prevalent form of gastrointestinal ischemia, accounting for 50-60% of all cases (1, 4), as well as the second most common cause for lower gastrointestinal bleeding, after diverticulosis (5, 6). Despite this, ischemic colitis has not been studied sufficiently and thus remains poorly understood. Moreover, previous studies have in large part not met the current standards in the diagnosis of ischemic colitis, as relatively few studies have requirements of histological confirmation of the diagnosis of ischemic colitis in every case (7).

To our knowledge, very limited data exist on the incidence of ischemic colitis in the general population and large-scale, population-based studies assessing the clinical course and outcome of patients with ischemic colitis are infrequently reported (8-11). Furthermore, studies evaluating factors related with the occurrence and recurrence of ischemic colitis are largely lacking (11-15). As a consequence, physicians are often presented with a challenge when guiding their patients with regard to modification of risk factors and when it comes to deciding whether patients with a risk of recurrent ischemic colitis should receive prophylactic management and what that treatment should consist of. Currently, the primary focus in preventing recurrence involves minimizing the impact of factors that may contribute to the development of ischemic colitis. However, more reliable and definite guidelines are needed.

1.1 Incidence and Gender Predilection

Overall, ischemic colitis is a relatively uncommon clinical identity in the general population. The incidence rate for ischemic colitis has been reported to range from 4.5 to 9.9 cases per 100.000 persons/year in the general population and 44 cases per 100.000 persons/year for those above 40 years of age (11). This accounts for an estimated 1 in every 2000 acute hospital admissions (16). However, the incidence rate of mild cases of ischemic colitis is presumably underestimated as they are often of transient nature, not requiring the patient to seek medical care and therefore go unreported. Furthermore, studies suggest that patients with ischemic colitis are commonly misdiagnosed as having other bowel disorders, notably inflammatory bowel disease or infectious colitis (17).

Although younger individuals may be affected, ischemic colitis is primary illness of the elderly with varying comorbidities. The average age at presentation is 70 years and approximately 90% of cases occur in patients over the age of 60 years (18, 19). With the continuing expansion of the elderly population, the incidence of ischemic colitis is expected to present a further increase in the future. The disease has been found to have a female predominance (11, 20), although some studies demonstrate the opposite (21). Furthermore, ischemic colitis has been reported to occur at a significantly younger age in males than in females (21, 22).

1.2 Vascular Anatomy of the Colon

An understanding of the colonic vascular anatomy is necessary when considering the pathophysiology and etiology of ischemic colitis (Figure 1). The colon and rectum derive their blood supply from branches of two major arteries, the superior mesenteric artery (SMA) and the inferior mesenteric artery (IMA), as well as branches from the paired internal iliac arteries. The SMA supplies the cecum, the ascending colon and proximal two-thirds of the transverse colon through the middle colic, right colic and ileocolic branches. In addition, the SMA supplies the entire small intestines except for the superior part of the duodenum. The IMA gives rise to the left colic and sigmoid arteries which supply the distal transverse colon, descending and sigmoid colon, and then it terminates as the superior hemorrhoidal artery which supplies the rectum. The rectum has a dual blood supply, also receiving blood from branches of the internal iliac arteries. As a consequence, the rectum is relatively resistant against ischemic insults (23, 24).

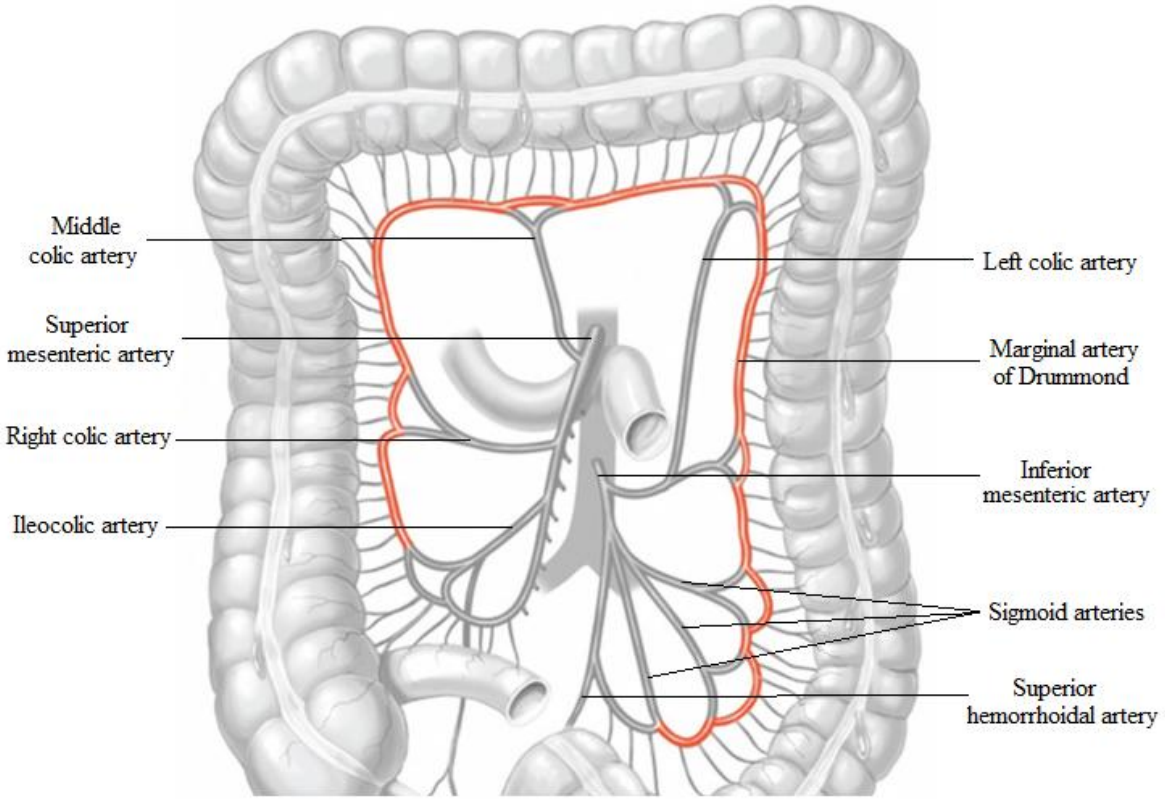

Figure 1 Vascular anatomy of the colon. The arc of Riolan and central anastomotic artery are not shown. This image was adapted from Quizlet LLC, 2014.

An extensive network of collateral blood vessels exists between the SMA, IMA, and iliac arteries. The arcades interconnect at the base of the mesentery, forming the arch of Riolan, central of the mesentery, forming the central anastomotic artery, and along the mesenteric border, forming the marginal artery of Drummond, from which vasa recta arise. This abundant collateral circulation provides the colon with a substantial protection from ischemic insults should any of the main vascular branches become occluded. During gradual occlusion of the main branches, the arch of Riolan or the central anastomotic artery may dilate and form the meandering artery to compensate for the decreased blood flow (25). Despite this vast collateral circulation, there are vulnerable points, called "watershed areas", located at the regions supplied by the most distal branches of the colonic arteries, where the collateral connections are narrow and may even be incomplete in some individuals. As a consequence, these "watershed" areas are particularly susceptible to ischemic insults when colonic blood flow decreases. The "watershed" areas include the splenic flexure, also known as Griffith's point, where the left branch of the middle colic artery and the ascending branch of the left colic artery meet via the marginal artery of Drummond. This important collateral connection between the SMA and IMA is diminutive or absent in up to 5% of the population, resulting in a 1.2-2.8 cm^2 region being devoid of vasa recta (26, 27). Another well-known "watershed area" is the rectosigmoid junction, also known as Sudek's point, where distal branches of the

IMA meet, specifically the last sigmoid branch and the superior hemorrhoidal artery. This anastomosis is often small and narrow, which places this segment of colon at a high risk for ischemic injury (28). The right colon is also a vulnerable point as the marginal artery of Drummond is poorly developed at that site in up to 50% of the population (29). As a result, the vasa recta are smaller and less developed in the right colon as compared to the left colon (30).

Although the most frequently affected segments, ischemic injury is by no means confined to the "watershed" areas and studies have shown that virtually any part of the colon can be affected (22). The left colon has been found to be the predominant location, accounting for approximately 75-85% cases, with an isolated splenic flexure involvement in nearly 25% cases (31, 32). Studies are not consistent regarding the frequency of a right colon involvement, with reports ranging from 10-46% (16, 21, 33). In some cases, the location of ischemia can give a clue as to what caused the disease. Localized, non-occlusive ischemia tends to affect the "watershed" areas of the colon, namely the splenic flexure and rectosigmoid junction, and ligation of the IMA normally leads to ischemic injury in the sigmoid colon. Isolated right colon involvement is mainly seen in patients with SMA disease, in systemic low-flow states and during repeated episodes of hypotension and major fluid shift such as in patients with chronic renal failure that requires hemodialysis. Conversely, more limited segments are typically involved during a thromboembolic event (4, 16).

1.3 Pathophysiology

Ischemic colitis is an inflammatory disease of the colon which develops when blood flow becomes inadequate to meet metabolic demands of the colon tissue, with resultant ischemic injury and a secondary inflammation. Any condition or factor that reduces colonic mean arterial blood pressure below 40 mmHg can lead to ischemic colitis (34). The blood flow may be compromised by alterations in the systemic circulation or by anatomic or functional changes in local colonic vasculature (32). Several factors are thought to render the colon more susceptible to these insults than any other part of the gastrointestinal tract. Firstly, the colon receives inherently lower blood flow than the remainder of the gastrointestinal tract, or about 20-25% of resting cardiac output (35, 36). Secondly, the colonic microvasculature plexus is less developed and is embedded within a relatively thicker wall as compared to the small intestine (32). Thirdly, colonic blood flow decreases during times of functional motor activity of the colon, such as during periods of increased peristalsis (35). Lastly, the colonic blood

flow appears to be highly sensitive to autonomic stimulation and can decline to 10% of cardiac output during times of physical and emotional stress (37).

As the mucosa is the most metabolic active layer of the colonic tissue, it is always the first part to be affected when colonic blood flow decreases. With prolonged compromise to the blood flow, ischemic changes will subsequently progress to the serous membrane (36, 38). The initial ischemic insult is the result of hypoxia due to reduction in blood flow but additional damage may occur when blood flow is re-established with resultant reperfusion injury (39). Reintroduction of blood flow causes a release of free radicals and reactive oxygen species which may cause severe cell damage and even lead to cell necrosis (40). Another phenomenon that may extend the ischemic insult is prolonged vasospasm as a result of decreased blood flow (41). Such sudden vasoconstriction may even persist long after the blood flow has returned to normal. The mechanism behind this response remains unclear, but studies suggest that the potent vasoconstrictor endothelin might play a role in the process (42).

1.4 Etiology

Ischemic colitis has been associated with numerous causes and risk factors, but is commonly classified into two groups based on two major causative mechanisms: occlusive and non-occlusive (32) (Table 1).

Table 1 An overview of causes of ischemic colitis.

Occlusive ischemic colitis	Non-occlusive ischemic colitis
Arterial	Idiopathic
Arterial thrombosis	Hypotension
Arterial embolus	Impaired cardiac output
Cholesterol embolization	Low-flow during surgery/hemodialysis
Atherosclerosis	Circulatory shock
Small vessel disease	Cardiogenic
Diabetec vasculopathy	Septic
Vasculitis	Hemorrhagic
Amyloidosis	Hypovolemia
Trauma	Dehydration
Iatrogenic cause	Hemorrhage
Aortic surgery	Strenuous physical activity
Cardiac bypass surgery	Medications
Venous	Colonic obstruction
Venous thrombosis	Severe constipation
Pancreatitis	Neoplasm
Portal hypertension	Volvuli
Hypercoagulopathies	Hernia

Occlusive disease can result from either arterial or venous obstruction, and occurs in most cases at an arteriolar level. Arterial obstruction is most commonly caused by atheroma, thrombus or embolus, the latter being frequently of a cardiac source, with reported occurrence rate in almost one-third of patients with ischemic colitis (43). Accordingly, major cardiovascular risk factors such as hypertension, dyslipidemia, diabetes mellitus, cigarette smoking and old age are frequently seen in patients with ischemic colitis. Diseases that promote embolization such as atrial fibrillation and myocardial infarction are also considered to be risk factors for the development of ischemic colitis (13). In addition, arterial obstruction may be related to microvascular diseases such as diabetic vasculopathy, vasculitis and amyloidosis, and is occasionally of traumatic or iatrogenic origin (44, 45). Occlusive ischemic colitis can also result from a venous obstruction, but this is not common. Venous causes include venous thrombosis, pancreatitis, portal hypertension and inherited or acquired hypercoagulation state. Accordingly, studies have reported abnormalities in coagulability in 28% to 72% of patients with ischemic colitis (46, 47). However, it is yet to be determined how important role increased coagulability plays in the pathogenesis of the disease.

Although ischemic colitis is occasionally associated with occlusion, development in the absence of major vasculature occlusion is far more common (32). Yet, the pathophysiology of non-occlusive ischemic colitis remains somewhat unclear. This is evident as a large group of patients develop ischemic colitis without any obvious precipitating event. Such spontaneous forms of ischemic colitis are normally viewed as an idiopathic localized forms of non-occlusive ischemia in association with small vessel diseases (48). In other cases, the non-occlusive ischemia can be identified as a consequence of systemic hypotension or hypovolemia. Hypotension can result from number of causes, such as impaired cardiac output due to myocardial infarction, congestive heart failure or cardiac arrhythmias; anti-hypertension medications; low-flow states during surgery or hemodialysis; and prolonged circulatory shock of any etiology (48, 49). Hypovolemia can be attributed to dehydration or hemorrhage (50). Either condition can trigger a mesenteric vasoconstrictive reflex with resultant vasoconstriction and reduced flow in colonic end arteries (51, 52). Likewise, strenuous physical activities, such as long-distance running and bicycling, can lead to ischemic colitis, presumably due to shunting of blood away from the colonic circulation, along with dehydration and electrolyte abnormalities (53). Various medications have also been implicated as contributing factors for the development of ischemic colitis, either by directly affecting the local or systemic vasculature or by causing severe constipation with resultant ischemic colitis. These medications include oral contraceptive pills, vasopressors,

diuretics, digitalis, appetite suppressants, chemotherapeutic agents, decongestants, immunosuppressive agents, statins, psychotropic medications, laxatives, interferon-α, danazol, non-steroidal anti-inflammatory drugs and 5-HT_3 receptor agonist and antagonist such as sumatriptan and alosetron (54-66). Additionally, ischemic colitis has been associated with illicit drug abuse, most notably cocaine and methamphetamine abuse (67, 68). Illicit drug abuse is especially prominent among young patients diagnosed with ischemic colitis. On rare occasions, increased intraluminal pressure due to mechanical obstruction may cause compression of the mucosal vessels and lead to non-occlusive ischemia proximal to the obstruction. As a result, severe constipation, neoplasm, volvuli, diverticulitis, stricture and hernias are all clinical condition that may precipitate ischemic colitis (69, 70). Moreover, for unclear reasons, patients with irritable bowel syndrome and chronic obstructive pulmonary disease seem to have an increased risk for ischemic colitis as compared to the general population (11, 70).

It should be noted, that even though referred as a non-occlusive disease, the colonic arteries are not necessarily normal. On the contrary, patients diagnosed with non-occlusive ischemic colitis, particularly elderly patients, frequently have pre-existing vasculopathies such as age-related tortuosity of the longer colic arteries and atherosclerosis of small vessels that may cause decreased perfusion and render the colon more susceptible to ischemic insults (18). Nevertheless, in all cases of non-occlusive ischemia, the final event leading to ischemic injury is not of vascular obstructive nature but rather associated with low-flow states or a vigorous vasoconstriction.

A special circumstance where ischemic colitis is of particular concern is following surgical procedures where both occlusive and non-occlusive compromise to the colonic blood flow may predispose the colon to ischemic injury. Ischemic colitis is estimated to occur in up to 6 % of patients following open aortic reconstruction and in up to 60% of patients following emergency surgery for ruptured abdominal aortic aneurysm (71-73). In these cases the distal left colon is virtually always involved due to iatrogenic ligation of the IMA or intraoperative hypotension combined with chronic occlusion of the IMA, in both instances in a setting of poor collateralization. Although not as common, with reported incidence rate under 0.2%, ischemic colitis may also follow cardiac bypass surgery. This is a live-threatening complication with a mortality rate of up to 85% (74, 75).

In conclusion, it is evident that ischemic colitis may be associated with innumerable conditions. However, what ultimately triggers an episode of ischemic colitis cannot be determined in most cases. This is especially true for spontaneous forms of ischemic colitis in

otherwise healthy individuals and when older, debilitated patients with history of various coexisting medical condition are diagnosed with the disease. In younger patients a definite cause is generally more easily recognized. In this group of patients, a certain number of conditions that predispose to ischemic colitis are especially prominent. These include vasculitides, medication such as estrogens and psychotropic drugs, cocaine and methamphetamine abuse, sickle cell disease, strenuous physical activity and inherited coagulopathies (76, 77).

1.5 Severity and Different Forms of Ischemic Colitis

The severity and consequences of ischemic colitis varies widely depending on the underlying cause, the degree of vascular obstruction, the rapidity of the onset of ischemia, the duration of ischemic insult, the extent of collateralization, the metabolic requirements of the affected bowel and comorbid conditions (16). The clinical and pathological manifestation can thus range in severity from mild, self-limited disease of transient nature characterized by superficial mucosal damage to acute fulminant ischemia which may progress to transmural infarction and even death. These manifestations can be patchy, involve the entire colon or, more frequently, they can have a segmental distribution. According to the classification of Brandt and Boley (16) ischemic colitis comprises the following distinctive clinical subtypes: (1) reversible ischemic colonopathy; (2) transient ischemic colitis; (3) chronic ulcerative ischemic colitis; (4) ischemic colonic stricture; (5) colonic gangrene; and (6) fulminant universal colitis. However, for simplicity, ischemic colitis is most often classified clinically as either gangrenous or non-gangrenous (32).

Non-gangrenous ischemic colitis is the most prevalent form of the disease, accounting for 80 to 85% of all cases. It only involves the mucosal and submucosal layer and often resolves either spontaneously or with conservative medical care. The non-gangrenous form can be further subclassified into transient, reversible forms with mild damage (50%) and chronic, irreversible forms with more severe injury (50%). These chronic forms include long-term complications such as chronic segmental colitis (20-25%) and stricture development (10-15%), the latter being a result of severe ischemia where the muscularis propria is replaced by fibrous tissue forming stricture (78). The gangrenous form accounts for the remaining 15-20% of cases. It is the most severe form of ischemic colitis and manifests as a full-thickness ischemia that may progress to a full-thickness necrosis, which may lead to perforation and even death if not treated early. Individuals with gangrenous ischemic colitis always require surgical intervention and have high morbidity and mortality rates (32).

1.6 Clinical Presentation

Ischemic colitis has a highly diverse clinical presentation depending on causality and severity. Nevertheless, the initial clinical presentation tends to be similar among all patients. The most frequently associated symptom is cramping abdominal pain, generally of abrupt onset. The pain is usually mild and although often poorly localized, ischemia involving the left colon tends to cause pain in the left lower abdominal quadrant and ischemia involving the transverse and right colon normally refers pain to the central abdomen. Abdominal pain is often accompanied by an urgent desire to defecate and diarrhea. Also, subsequent development of hematochezia normally follows within 24 hours from symptoms onset. The blood is frequently mixed with stool and may either be bright red or maroon colored (39). The bleeding is usually not profuse and rarely causes hemodynamic instability. Significant blood loss requiring transfusion should therefore indicate an alternative diagnosis (16). Other less common symptoms include anorexia, nausea, vomiting or abdominal distention as a result of an associated ileus. Clinical examination of the abdomen often reveals mild-to-moderate tenderness over the involved segment and rectal examination generally reveals positive hemoccult. If ischemia leads to transmural infarction, then peritoneal signs of guarding and rebound tenderness may be present on clinical examination. Patients with such an advanced disease commonly present with fever, leukocytosis, metabolic acidosis and septic shock as well. Fortunately, this is a rare finding as most patients with ischemic colitis do not have a transmural infarction. Chronic forms of ischemic colitis may also cause symptoms. Strictures may manifest several months later with obstructive symptoms such as abdominal distention and constipation, while patients with chronic segmental colitis tend to present with chronic abdominal pain, persistent diarrhea, rectal bleeding, and/or weight loss (32, 39).

1.7 Diagnosis

Establishing a correct diagnosis of ischemic colitis often remains a challenge, as the initial clinical presentation of the disorder is generally vague and nonspecific. There are no widely accepted diagnostic criteria for ischemic colitis. The diagnosis depends largely on early and repeated evaluation of the patient’s clinical status in combination with history taking, biochemical findings, radiological studies, endoscopic evaluation and histological assessment.

1.7.1 Clinical Evaluation

High index of clinical suspicion is fundamental for the diagnosis of ischemic colitis. When individuals present with abdominal pain, diarrhea and hematochezia, ischemic colitis should always be considered as a potential cause. The clinical settings upon which these symptoms appear can be of important value and further raise the clinician's suspicion. The presence of well-known precipitating conditions should therefore be taken notice of. This includes abuse of illicit drugs, strenuous physical activity, recent cardiac or aortic surgery, major cardiovascular risk factors and diseases as well as colonic obstruction disorders.

1.7.2 Biochemical Findings

In terms of laboratory studies for accurate diagnosis of ischemic colitis, various biochemical markers have been investigated. However, none has been found sufficiently specific or reliable, so laboratory studies remain of minor clinical importance. Nevertheless, leukocytosis is a common finding and elevated levels of lactate, inorganic phosphate and alkaline phosphatase along with metabolic acidosis indicate significant ischemic injury (79). Unfortunately, these changes usually develop late in the course of the disease, so markers predicting early or mild stage ischemia are greatly needed.

Studies exploring serum levels of the stereoisomer D-lactate have shown some promise in identifying a reliable predictor of early colonic ischemia, with a reported 82%-90% sensitivity and 77%-87% specificity (80, 81). D-lactate is a metabolic by-product of the normal anaerobic bacterial flora in the gastrointestinal tract. When the colon suffers ischemic injury the intestinal mucosa becomes more permeable, allowing D-lactate to enter the blood circulation. Since the liver is unable to metabolize D-lactate, an increase in serum levels of D-lactate occurs (82, 83). Although promising, these laboratory studies have yet to be incorporated into routine clinical practice.

1.7.3 Radiological Studies

Plain radiographs are of limited use in the diagnosis of ischemic colitis. In about 20% of cases, the films reveal signs suggestive of ischemia, these include thumbprinting, colonic dilation, mural thickening or pneumatosis coli, the latter being a sign of more severe damage with passage of gas into the colon wall (84). However, these findings are nonspecific and warrant further evaluation. The main indication for performing a plain radiography is to exclude perforation with evidence of pneumoperitoneum, as that would require aggressive actions.

Computed tomography (CT) is frequently performed during an initial assessment of patient presented with nonspecific abdominal pain. It can be very useful as it may localize the site of colitis, exclude other conditions that may present similarly to ischemic colitis and thus limits differential diagnosis possibilities, and finally, identify complications. Unfortunately, CT findings cannot be used to accurately evaluate or predict the development of infarction. When patients present with non-gangrenous form of ischemic colitis, CT images often reveal segmental bowel wall thickening, thumbprinting, and pericolonic fat stranding, with or without peritoneal fluid. CT images may also show the double halo or target sign, in which the outer mural layer enhances with intravenous contrast, while there is a inner mucosal hypoperfusion. After reperfusion, the sign may be produced by submucosal edema or hemorrhage. If there is a complete arterial occlusion, the colonic wall will remain thin and unenhancing due to no reperfusion. In these cases, thrombus or emboli in a corresponding artery may also be seen. With more advanced disease, CT scans may reveal pneumatosis coli, pneumoperitoneum or air within the mesenteric or portal venous system, all of which are suggestive signs of infarction (33).

Barium enema has been found predictive of ischemic colitis in up to 75% cases by demonstrating thumbprinting, pseudopolyps, ulcers, ridges, edema and strictures, but all of these findings are nonspecific (85). Because of the pressure exerted on the colon there is a risk of exacerbating the ischemic insult with overdistention of the colon. In addition, barium enema can make subsequent use of angiography, CT, or colonoscopy difficult because of residual contrast agent (39). As a consequence, barium enema has essentially been replaced by CT scanning and colonoscopy in acute settings. Nevertheless, barium enema still remains useful when assessing chronic complications of ischemic colitis such as stricture formations.

Color Doppler ultrasonography may be helpful in recognizing ischemic colitis and differentiating it from inflammatory bowel disease. An absent or barely visible color Doppler flow strongly suggests ischemic colitis and inflammatory bowel disease should practically be excluded. However, ultrasonography has limited utility due to operator-dependent quality, overlying bowel gas and poor sensitivity for low-flow vessel disease (86).

Angiography is generally not indicated as part of the diagnosis of ischemic colitis. This is because large mesenteric vessel occlusion is rarely the underlying cause, much rather the ischemia is at an arteriolar level. Furthermore, transient hypoperfusion is the hallmark of most cases of ischemic colitis, so blood flow has usually returned to normal by the time of evaluation. Nevertheless, angiography can be very helpful when acute mesenteric ischemia needs to be excluded such as in cases of isolated right-sided colitis (32).

Overall, the gross morphologic features of ischemic colitis demonstrated with radiological imaging are nonspecific and may be seen in other types of colitides (84). Moreover, all of the studies above may reveal normal findings in mild cases of ischemic colitis or if done early in the course of the disease. As a consequence, radiological studies remain of limited value in the diagnosis of ischemic colitis.

1.7.4 Endoscopic Evaluation

Endoscopy has become the gold standard for establishing diagnosis of ischemic colitis as it is the most sensitive and specific diagnostic modality available. It allows visual inspection of the colonic mucosa and biopsy sampling for histological assessment. During endoscopy, caution must be taken not to overinflate the colon because overdistenstion can further reduce colonic blood flow and thus potentially aggravate the ischemic damage. In this regard, insufflations with carbon dioxide are preferable over room air, as carbon dioxide is more rapidly absorbed and has a vasodilatory effect (87). Also, if signs of gangrene are present, colonoscopy should not be advanced beyond the affected area due to a great risk of perforating the fragile infracted colon wall. Total colonoscopy is generally the preferable method of endoscopy because 30-40% of cases occur beyond the level reached by flexible sigmoidoscopy (88). Yet, in some cases, flexible sigmoidoscopy is considered to be more appropriate. This applies to ischemic colitis following aortic surgery or aortic aneurysm rupture, where the left colon is almost invariably affected and full colonoscopy may be harmful (89, 90).

The findings at endoscopy depend on the stage and severity of ischemic injury. Early in the course of the disease, endoscopy usually reveals pale-appearing and edematous mucosa with interspersed areas of petechial hemorrhages or superficial ulceration. The characteristic colon single-stripe sign may be present as well, demonstrated as a single inflamed or ulcerated colon strip oriented along the longitudinal axis of the colon (91). As the ischemia progresses to the submucosa, bluish-black hemorrhagic nodules may appear. These lesions represent the characteristic thumbprinting seen on radiographic studies. The submucosal hemorrhages usually resolve within days as reabsorption or sloughing occurs. Endoscopy should therefore be performed soon after the onset of symptoms, preferably within the first 48 hours, to ensure maximum effectiveness of the procedure. It may be difficult to identify transmural infarction as only the mucosa can be examined at endoscopy. However, a cyanotic, gray-green or even black mucosa is highly suggestive of gangrenous ischemic colitis. Finally, at chronic stages, endoscopy may reveal strictures, decreased haustration and mucosal granularity. Again, all of these findings are nonspecific and must, therefore, be considered in appropriate clinical

context. Still, a segmental involvement, rectal sparing and clear transition between affected and non-affected tissue is highly suggestive of ischemic colitis (31, 92).

The histological changes of ischemic colitis are mostly nonspecific (Figure 2). They include vascular congestion, edema, hemorrhage, ulcerations, mixed inflammatory infiltration and exudate, hyalinized lamina propria and withered or atrophic crypts. However, two pathognomonic findings for ischemic colitis exist: superficial mucosal infarction and the presence of ghost cells (3, 32).

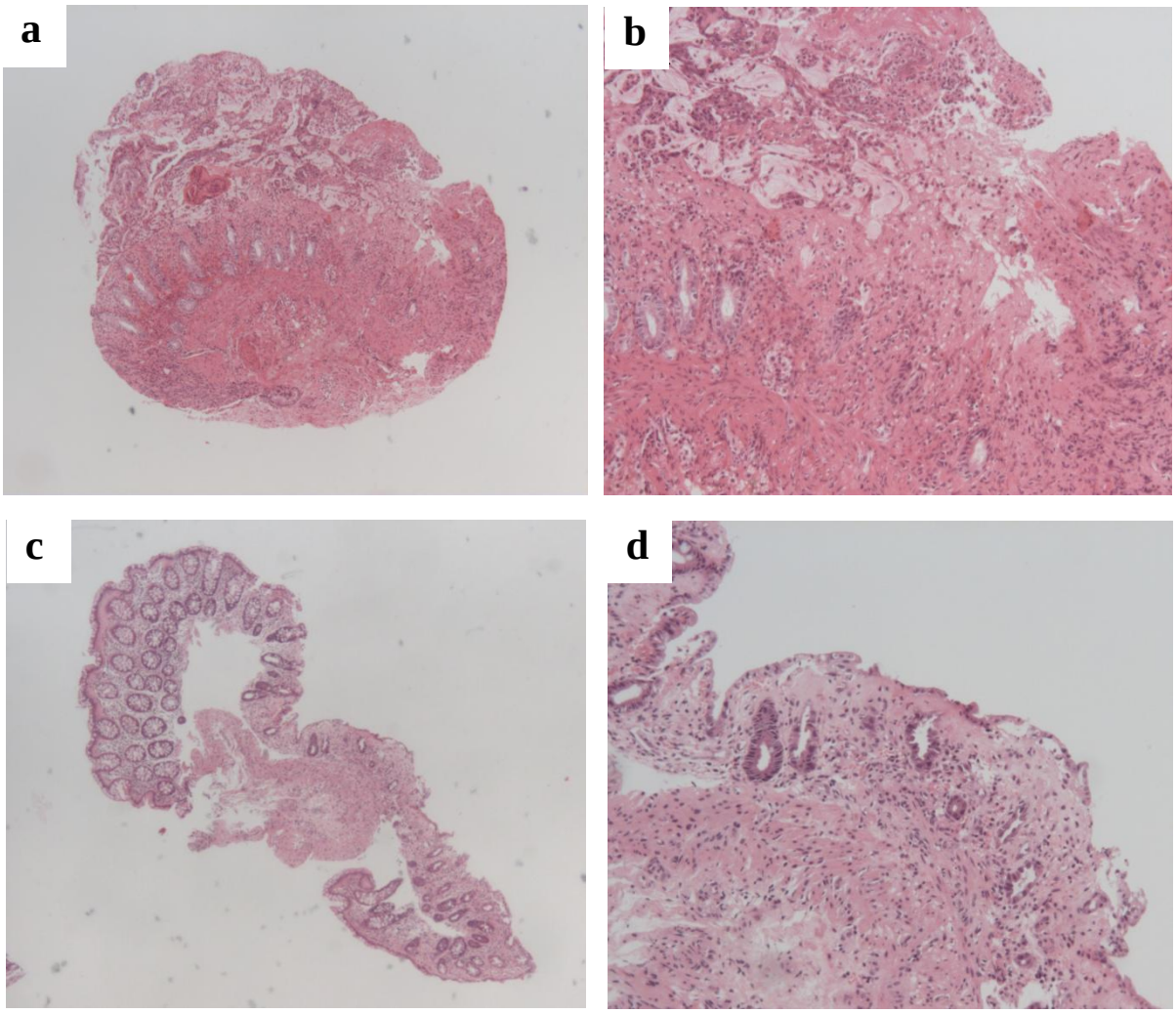

Figure 2 Histological findings of ischemic colitis (H-E staining). **a** Superficial mucosal necrosis with loss of surface epithelium, hyalinized lamina propria, atrophic crypts, inflammatory exudates and pseudomembrane (original magnification x 10). **b** Same view as **a**, at different magnification (original magnification x 20). **c** Normal colonic tissue on the left but ischemic inflammation on the right with superficial mucosal necrosis with loss of surface epithelium, hyalinized lamina propria and atrophic crypts (original magnification x 10). **d** Same view as **c**, at different magnification (original magnification x 20). These images were obtained from the Department of Pathology at the National University Hospital of Iceland.

1.7.5 Differential Diagnosis

The differential diagnosis of ischemic colitis is broad and includes infectious colitis, inflammatory bowel disease, pseudomembranous colitis, diverticulosis, diverticulitis, colon carcinoma, peptic ulcer disease, bowel obstruction, acute pancreatitis and colon carcinoma. Also, in cases when the right side of the colon is affected or if patient‘s clinical presentation is unusually severe, acute mesenteric ischemia has to be excluded (32).

1.8 Management

Management of ischemic colitis depends on the severity of the disease. Majority of patients present with transient non-gangrenous colitis that usually resolves spontaneously or can be successfully managed conservatively. However, urgent surgical intervention is critical for patients presented with signs of transmural infarction and/or perforation. Since the initial clinical presentation is not predictive of the severity and the course of the disease, it may be difficult to estimate which patients will need surgery (32).

In milder cases, minimizing the impact of factors that may contribute to ischemia and optimizing intestinal perfusion is fundamental. A combination of intravenous fluids and bowel rest is advised to maintain adequate colonic perfusion and keep the intestinal oxygen demand at minimum. Parenteral nutrition is recommended for patients who need prolonged bowel rest and are considered poor candidates for surgery (93). Cardiac function and oxygenation should be optimized. Whenever possible, the inciting cause should be mitigated or removed immediately. Discontinuation or avoidance of medications known to cause mesenteric vasoconstriction is therefore recommended. Whenever an ileus is present or the colon is notably distended, a nasogastric tube or rectal tube should be placed, respectively. In moderate or severe cases, patients are often given empiric broad-spectrum antibiotics that provide coverage for the normal bacterial flora of the colon. Although there is no clinical evidence of the beneficial effect of antibiotic administration in the treatment of ischemic colitis, it is considered by some clinicians to be effective since ischemia may cause disruption of mucosal integrity and thereby increase the risk of bacterial translocation and potential progression to multiple organ failure (94). Furthermore, animal experimental studies have demonstrated that antibiotic administration reduces the extent and severity of colon damage (95). Nevertheless, randomized controlled studies on humans are lacking. Systemic corticosteroids are contraindicated as they might obscure signs of peritoneal irritation and postpone necessary surgical intervention. Oral cathartics and bowel preparations prior to colonoscopy or surgery should be avoided, due to a risk of perforation and toxic dilation (32).

Careful monitoring should follow with repeated assessment of patient's clinical status along with serial imaging and endoscopic examinations if there is no clinical improvement within 24-48 hours. An exploratory laparotomy and bowel resection is indicated if patients show signs of clinical deterioration. These signs include persistent fever, marked leukocytosis, a development of acidosis, protracted bleeding, peritoneal irritation, colonic distention septic shock and radiological or endoscopic evidence of transmural infarction (16).

About 20% of patients diagnosed with ischemic colitis will require surgery. In acute settings, signs of advanced disease with transmural infarction or perforation, such as peritoneal signs and massive bleeding, prompt an immediate surgical intervention. In subacute settings, surgery may be indicated in patients with no improvement in clinical condition despite conservative management or those who develop protein-loosing enteropathy. (16).

During surgery, the serosal surface of the colon may appear well perfused even if an extensive mucosal damage is present. To ensure resection of all affected bowel, it is therefore imperative to use preoperative imaging or endoscopic assessment of the colitis distribution as a reference and always check for viability of the mucosal margins of the resected segment (96). In some cases, a temporary abdominal closure with planned second-look laparatomy within 24 hours is appropriate, as additional resection is sometimes required due to ongoing ischemia (97). Majority of patients who undergo surgery will have a subtotal or segmental colectomy with an end colostomy or ileostomy, where the distal bowel is either fashioned into a mucous fistula or closed to form a Hartman pouch (98). The stoma may have to be permanent depending on the extent of colon involvement and patient's health status, but if it is to be closed, it is usually done around 4-6 months after surgery when the patient has fully recovered (99). Creation of a primary anastomosis is usually not advised due to a great risk of leakage and poor general condition of patients. Nevertheless, in some cases, a primary anastomosis after a partial colectomy is an option. This applies when the patients are hemodynamically stable and the resected margins are distinctly well vascularized (97).

Elective surgery is occasionally recommended for patients suffering from symptomatic colonic strictures or chronic segmental colitis (100). However, in elderly patients with a high operative risk, endoscopic dilation may be preferable over surgery in management of colon strictures (101). Intervention is not always necessary though, as in some cases colon strictures resolve spontaneously within 12-24 months (21).

1.9 Prognosis

The overall outcome of patients with ischemic colitis rests on numerous factors, including severity of the disease, comorbidities, prompt diagnosis and appropriate medical care. Approximately 80% of patients will be successfully managed conservatively with an improvement in signs and symptoms within 24 to 48 hours and a complete clinical, radiological and endoscopic recovery within 2 weeks (32). These are patients with reversible form of non-gangrenous ischemic colitis. They hold a good prognosis and will not require any further therapy, although a follow-up colonoscopy is recommended to monitor progression or confirm complete recovery. More severe, but still reversible, ischemic injury may take one to six months to resolve (16).

Although most patients make a full recovery, approximately 30-40% of patients will develop chronic forms of ischemic colitis, some of which will be symptomatic and require surgical intervention. Surgical removal of the affected segment is usually curative and patients rarely develop ischemic colitis thereafter (100).

Patients who develop gangrenous form of ischemic colitis are generally more critically ill. They have substantially higher morbidity and mortality rates despite aggressive management which usually involves surgical intervention. The overall reported mortality rate of ischemic colitis is around 22% (102), however, for those who have infracted colon the mortality rate has been reported to be as high as 60% (16, 21). Comorbidities, late diagnosis and delayed or inadequate medical intervention may contribute to even higher mortality. Studies have shown that those with isolated right-sided ischemia have more severe disease as compared to those with ischemia isolated to other areas. This includes longer hospitalizations, a greater need for surgery and a higher mortality rate (7). Likewise, conditions such as absence of hematochezia, chronic renal failure requiring hemodialysis or development of ischemic colitis following cardiac and aortic surgeries or in association with myocardial infarction, have all been implicated with more severe disease (74, 103-105).

Finally, a minority of patients who recover from their initial ischemic event will experience recurrence of the disease. This area has not been investigated thoroughly, but the five-year rate of recurrence has been reported to range from 10% to 16% (22, 106).

2 Aims

The aim of the current study was to analyze patients with histologically confirmed diagnosis of ischemic colitis. The aim was fourfold:

1. Determine the incidence of ischemic colitis in a population-based setting
2. Evaluate the prevalence of implicated risk factors for the development of ischemic colitis in patients diagnosed with ischemic colitis
3. Observe clinical manifestations among patients diagnosed with ischemic colitis
4. Analyze immediate and long-term clinical outcomes of patients diganosed with ischemic colitis. This included identifying independent factors predictive of poor outcome and recurrence as well as evaluating patients' prognosis with respect to management and mortality from ischemic colitis or other diseases

3 Materials and Methods

3.1 Study Design

A retrospective study was conducted using data from medical records.

3.2 Case Finding Strategies

The study population consisted of individuals, aged 18 years and over, who were admitted to the National University Hospital of Iceland and the Akureyri District Hospital with ischemic colitis, during a 5-year period from January 1st 2009 through December 31st 2013. These two hospitals are the only hospitals in Iceland where patients are hospitalized for ischemic colitis. All patients with a clinical suspicion of ischemic colitis were identified by search for ICD-10 codes compatible with ischemic colitis (K52.9, K55.0, K55.1, K55.2, K55.8, K55.9) in the diagnosis database and for the term "ischemic colitis" in the text of electronic medical records. The database of the Department of Pathology was also screened for histological diagnosis of ischemia in the colon (SNOMED codes T67-M54200/M40700).

Medical records of all patients identified in the aforementioned search were thoroughly reviewed manually to identify patients with a potential diagnosis of ischemic colitis. A histological confirmation of ischemic colitis was required for participation. Specimens obtained during endoscopy, surgery or autopsy, were therefore reviewed by two pathologists at the National University Hospital of Iceland. Widely accepted histological criteria were used for the histopathological diagnosis of ischemic colitis. The histological findings were divided into those considered definite and compatible. Definite histology was defined as detection of superficial mucosal necrosis with loss of surface epithelium, hyalinized lamina propria, withered or atrophic crypts, inflammatory exudate and pseumembranes and/or hemorrhage into the lamina propria. Compatible histology was defined as detection of superficial mucosal necrosis and withered crypts accompanied by a few or none of the other microscopic findings listed above. These two histological groups were compared for age, gender, co-existing medical conditions and clinical characteristics.

Patients who developed colonic ischemia secondary to thromboembolic event in the SMA or IMA, vascular procedures, trauma or colonic obstruction, such as volvuli, hernia or colon carcinoma, were excluded from the study. Moreover, for accurate calculation on the incidence of ischemic colitis in Iceland, individuals who did not have a registered home in Iceland were excluded. After applying exclusion criteria, the study cohort comprised 89 patients, who had 96 cases of ischemic colitis from 2009 through 2013. Seven patients had both an initial episode of ischemic colitis and recurrence during the study period and six

patients had initially been diagnosed with ischemic colitis prior to the study period but relapsed between 2009 and 2013. For the statistical analyses in the current study, qualities of relapse episodes were described for those who experienced recurrence but data from the initial episode were used for the remainder of the study population. The initial and the relapse episodes usually had similar manifestation, but in some cases the manifestation was more severe at relapse and that information would be lost if only qualities of initial episodes were documented. Also, if each case were to be viewed separately, the data would be correlated, with resultant bias in analytical analyses. As a consequence, this was considered to be the best strategy for handling the data, as it describes the clinical characteristics of the study population with the highest accuracy possible while bias in analytic analyses is kept at minimal. However, for the analytical analysis, where predictive factors for recurrence were analyzed, data from all initial episodes were used, except for cases of severe ischemic colitis as those patients do not develop the disease again thereafter. Finally, in calculations of incidence rate, only data for those who had an initial episode during the study period were used. Age- and gender adjusted incidence rate was calculated based on numbers of Icelandic residents, 18 years and older, from 2009 through 2013 provided by the Statistics Iceland.

3.3 Data Collection

Electronic medical records of patients who fulfilled the pre-determined criteria for the diagnosis of ischemic colitis were retrieved and adequate information obtained from: laboratory investigations, endoscopy and pathology reports. Data were gathered on patients' baseline characteristics, which included age, gender, cigarette smoking habits and the following co-existing medical conditions: hypertension, diabetes mellitus, ischemic heart disease, heart failure, atrial fibrillation, cerebrovascular disease, peripheral arterial disease, chronic renal failure, a history of cancer, chronic obstructive pulmonary disease and hyper-cholesterolemia. Data on clinical presentation at admission were obtained for the following clinical symptoms and signs: abdominal pain, hematochezia, diarrhea and nausea/vomiting, abdominal tenderness, abdominal distension and signs of peritonitis, blood pressure, heart rate and temperature. Hypotension was defined as systolic blood pressure lower than 90 mmHg, tachycardia as heart rate greater than 90 beats/min and fever as temperature greater than 38°C. The following laboratory parameters obtained at admission were also extracted from patients' records: Hemoglobin (g/L), platelet counts (x109/L), creatinine (μmol/L), prothrombin time (PT) (sec), and international normalized ratio (INR). Clinically significant bleeding was defined if at least one of the following applied: hemoglobin < 100 g/L, patient required blood

transfusion or patient was admitted to the intensive care unit. Patients were classified as having either right colon involvement, left colon involvement, or both according to findings during endoscopic and/or surgical procedures. The form of ischemic colitis was documented as well. The disease was considered to be gangrenous if histological examination suggested mural infarction, transient if patients reported clinical resolution during the follow-up and chronic if patients sought medical attention due to persistent abdominal symptoms within three months of the initial hospitalization. Data were collected on management with regard to conservative treatment or surgery, the latter being further sub-classified as either immediate if performed within 24 hours of admission or delayed if performed later during the initial hospitalization. Immediate and long-term outcomes were recorded, which included poor outcomes, defined as need for surgical intervention and/or in-hospital mortality regardless of treatment modality. Furthermore, recurrence, defined as another episode of ischemic colitis at least three months after the initial episode with intermittent clinical resolution, was analyzed along with subsequent non-gastrointestinal vascular events, such as myocardial infarction or cerebrovascular events, and prognosis with respect to conservative treatment, surgery and mortality from ischemic colitis or other diseases.

3.4 Ethical Aspects

The study was approved by the Bioethics Committee and the Data Protection Authority of Iceland

3.5 Statistical Analysis

Continuous variables are presented as means (±standard deviations) and categorical variables are presented as absolute numbers (percentage) of patients with specific characteristic. All statistical analyses were performed using R computer software, version 3.0.2 (The R foundation for Statistical Computing, Vienna, Austria). In order to compare the two histological groups and assess independent factors predictive of poor outcome and recurrence, variables were evaluated using univariate and multivariate analyses. For univariate analysis, unpaired Student’s t-test was used for continuous variables and Fisher’s exact test for categorical variables. For multivariate analysis, a logistic regression model with a backward stepwise selection was constructed. Adjusted odds ratios and 95% confidence interval were calculated. Statistical significance was designated as a probability value of less than 0.05. All probability values were based on two-sided tests.

4 Results

4.1 Incidence

Eighty-nine consecutive patients fulfilled the pre-determined criteria for the diagnosis of ischemic colitis and were included in the study. However, only 83 patients were included in calculations of incidence wherein individuals who only had a relapse episode during the study period were excluded. The mean crude incidence rate of ischemic colitis over the study period was 6.9 cases per 100.000 inhabitants, 18 years and older, per year (95% confidence interval: 4.8-9.1). The mean age- and gender adjusted incidence rate of ischemic colitis was 7.3 cases per 100.000 inhabitants, 18 years and older, per year (95% confidence interval: 5.0-9.7). The specific adjusted incidence rates for each year are demonstrated in Figure 3. The adjusted incidence rates were stable during the 5 year study period. Age-standardized incidence rates for certain age groups are shown in Table 2. The highest incidence rate was observed in the oldest age group and the incidence rate was higher for those aged 40 years and over than for those younger than 40 years old ($p<0.0001$). Gender-standardized incidence rates are shown in Table 3. The incidence rate was higher among females than males ($p=0.0030$).

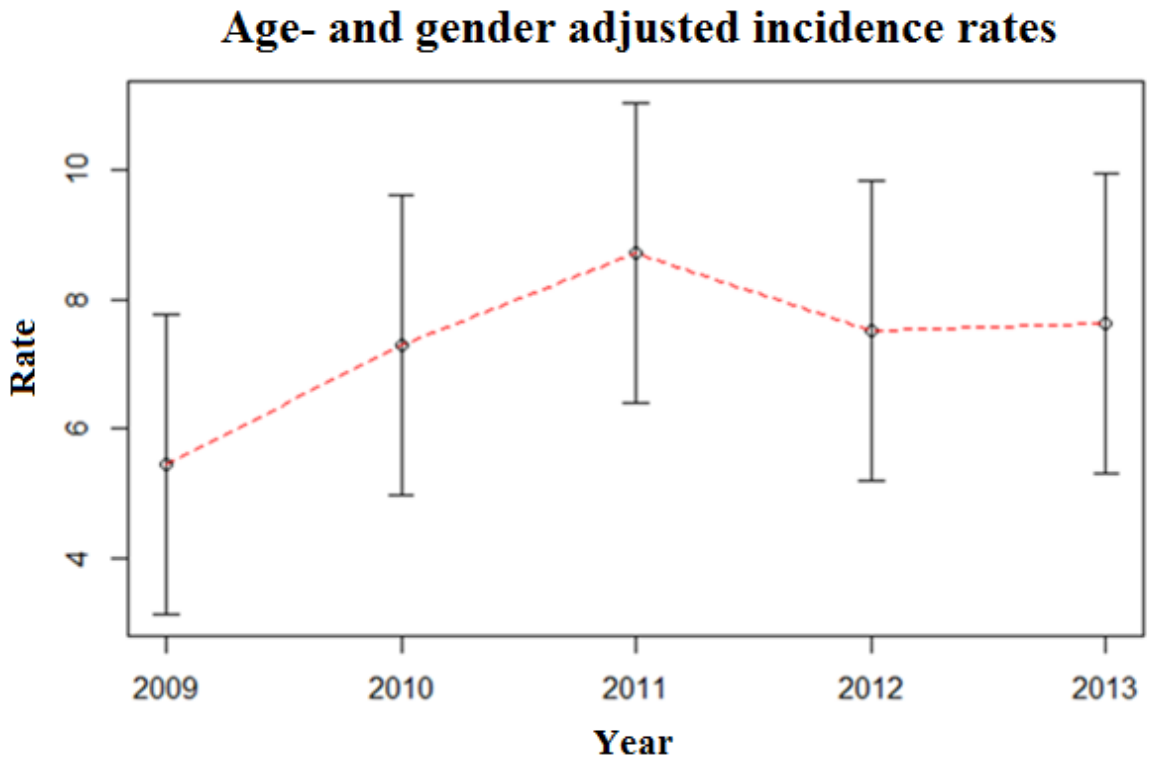

Figure 3 Age-and gender adjusted incidence rates over the study period for Icelanders, 18 years and older.

Table 2 Age-standardized incidence rates for certain age groups.

Age groups	Incidence rate (per 100.000/year)
20-29	2.1
30-39	1.4
40-49	3.2
50-59	5.5
60-69	13.8
70-79	28.1
80-89	25.5
90-99	38.3

Table 3 Gender-standardized incidence rates for Icelanders 18 years and older.

Gender	Incidence rate (per 100.000/year)
Female	10.4
Male	3.5

4.2 Demographics

Of the eighty-nine patients included in the study there were 61 women and 28 men (69% vs. 31%, ratio 2.2:1). The mean age of the study population was 65 years (± 16.7). The female patients were older than the male patients. The mean age of females was 68 years (±14.1) but for males the mean age was 59 years (±20.1) (p=0.0170). Eight patients were younger than 40 years of age, six of them were males. The age distribution by gender is shown in Figure 4.

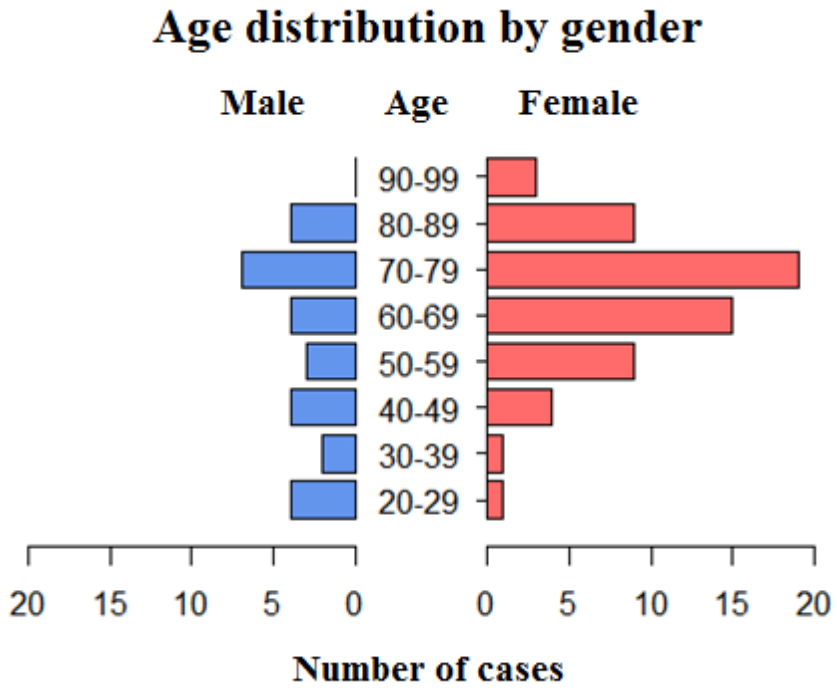

Figure 4 Age distribution of patients with ischemic colitis by gender.

4.3 Comorbidities and Life Style Habits

A total of 62 patients (70%) were reported to suffer from co-existing cardiovascular disease. Hypertension was the most commonly reported cardiovascular condition (n=55, 62%), followed by ischemic heart disease (n=19, 21%), atrial fibrillation (n=11, 12%), heart failure (n=6, 7%), cerebrovascular disease (n=8, 9%) and peripheral arterial disease (n=5, 6%). Other common co-existing medical conditions included diabetes mellitus (n=7, 8%), chronic obstructive pulmonary disease (n=13, 15%), chronic renal failure (n=5, 6%), history of cancer (n=12, 13%) and hypercholesterolemia (n=26, 29%). Some patients had several co-existing medical conditions, while a total of 20 patients (23%) had none of the investigated comorbidities listed above. Figure 5 illustrates comorbidities among the patients.

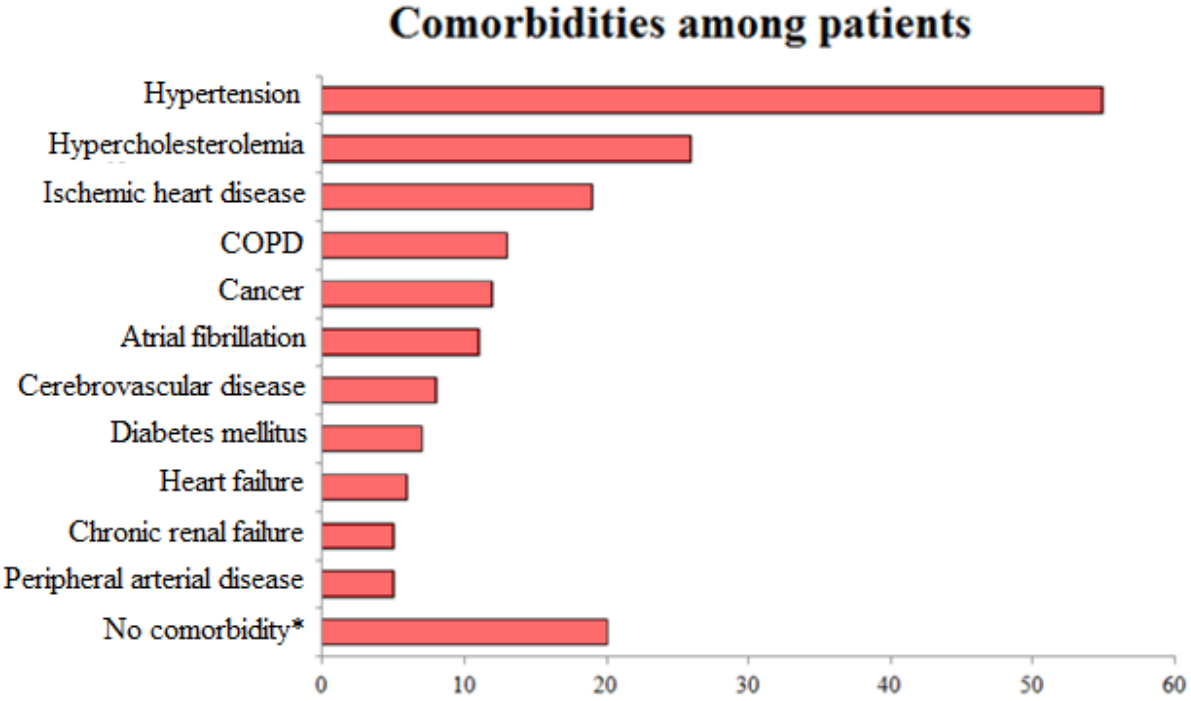

Figure 5 Comorbidities among patients with ischemic colitis. Some patients had several of the co-existing medical conditions investigated in the current study. COPD, chronic obstructive pulmonary disease.

More than half of the patients had a history of cigarette smoking. A total of 22 patients (25%) were active smokers and 33 patients (37%) were ex-smokers. Cigarette smoking habits were unknown in 10 patients (11%). The patient's cigarette smoking habits are depicted in Figure 6. A total of 7 patients (8%) had none of the investigated comorbidities listed above nor history of cigarette smoking.

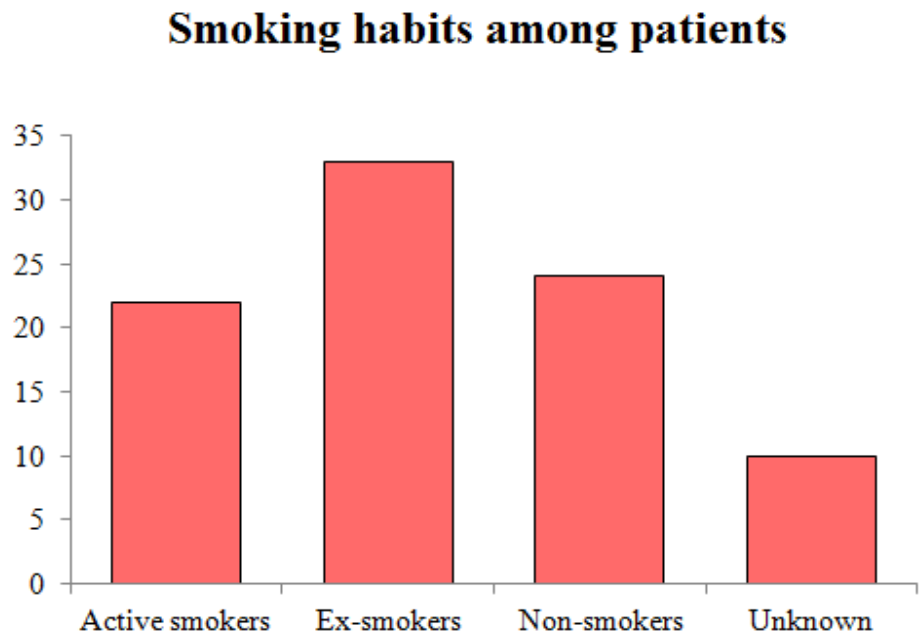

Figure 6 Cigarette smoking habits among patients with ischemic colitis.

4.4 Clinical Presentation

Symptoms, signs and laboratory study findings on admission are demonstrated in Table 4. The most commonly presenting symptom was abdominal pain, followed by hematochezia, persistent diarrhea and vomiting/nausea. The distribution of the three most frequent symptoms among the patients can be seen in Figure 7. Clinically significant gastrointestinal bleeding was a relatively rare finding among patients presented with hematochezia (n=14, 16%). Regarding vital sign assessment, only two patients presented with shock, while tachycardia and fever were observed more frequently. At physical examination, abdominal tenderness was observed in nearly all patients, whereas only ten patients presented with abdominal distension and seven patients showed signs of peritonitis.

Table 4 Symptoms, signs and laboratory studies among the study population.

Symptoms, signs and laboratory findings	n = 89
Abdominal pain	83 (93%)
Hematochezia	80 (90%)
Diarrhea	66 (74%)
Vomiting/Nausea	54 (61%)
Shock	2 (2%)
Tachycardia	37 (42%)
Fever	8 (9%)
Abdominal tenderness	80 (90%)
Abdominal distension	10 (11%)
Signs of peritonitis	7 (8%)
Hemoglobin (g/L)	140 (±20.1)
Platelet (x10/L)	260 (±112.6)
Creatinine (mmol/L)	95 (±49)
PT (sec)	14.9 (±2.9)
INR	1.4 (±0.6)

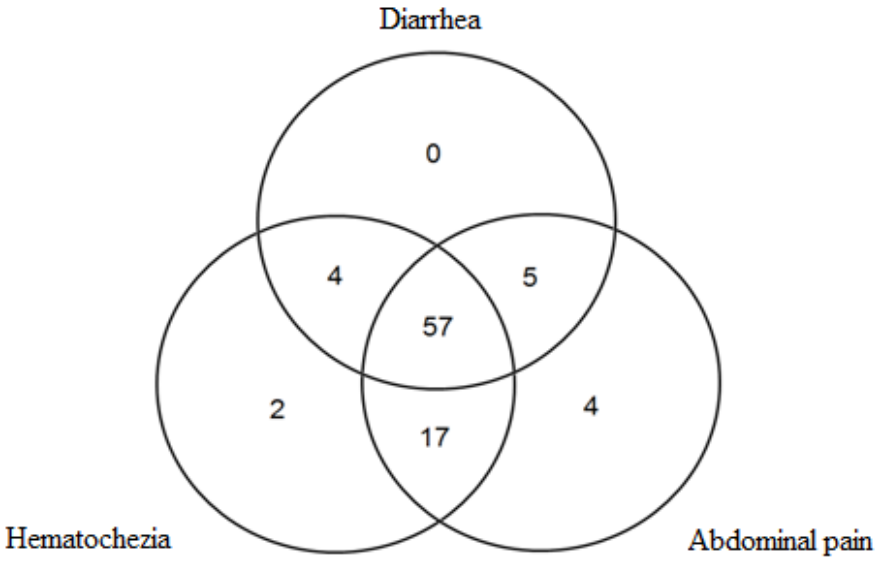

Figure 7 Distribution of abdominal pain, hematochezia and diarrhea among patients with ischemic colitis.

4.5 Form and Location of the Disease

Majority of patients presented with transient colitis (n=73, 82%), while gangrenous colitis was seen in only 10 patients (11%), three of whom had colon perforation. Chronic colitis was observed in 6 patients (7%) but no patients subsequently developed symptomatic stricture. Overall, no part of the colon was spared involvement. Ischemia was localized in the left colon in 78 patients (88 %), the right colon in 5 patients (6%), and affected both sites in 6 patients (7%) (Figure 8).

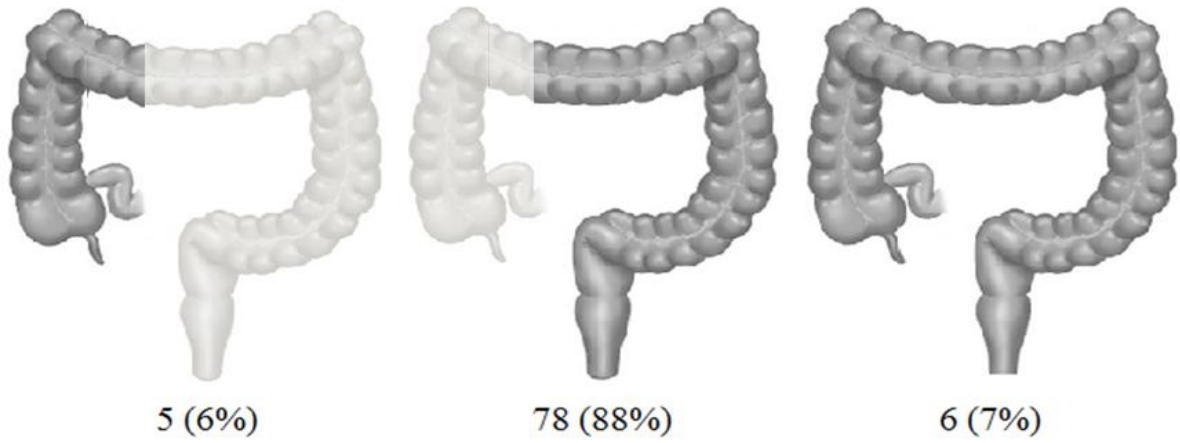

Figure 8 Location of involved colon segments among the study population. These images were adapted from Quiroz, F. Tratado de Anatomia Humana, 38. Edition, 2002.

4.6 Diagnosis

Almost all patients had endoscopy as a part of the diagnostic process regardless of treatment modality (n=85, 96%), 52 patients (61%) had flexible sigmoidoscopy, while full colonoscopy was performed in 36 of them (42%). Three patients underwent both types of endoscopy during the same hospital stay. Of the eight patients who underwent surgery, a prior endoscopy was performed in five patients. The diagnosis of ischemic colitis was established by biopsies obtained during colonoscopy in 80 patients (90%), during surgery in eight patients (9%) and during autopsy in one patient (1%). Based on histological findings, the overall diagnosis of IC was definitive in 63 cases (71%) and compatible in 26 (29%) cases. Comparison of characteristics between the two histological groups showed no significant difference regarding age, gender, comorbidities and clinical characteristics (data not shown).

4.7 Management

A diagrammatic summary of the management and clinical outcome, both immediate and long-term, is shown in Figure 9. During the study period, a total of 83 patients experienced ischemic colitis for the first time. Majority of these patients were treated with conservative management (n = 74, 89%), which consisted mainly of bowel rest, intravenous hydration and pain control. However, a total of eight patients required surgical intervention (10%). Five patients underwent immediate emergency surgery within 24 hours of admission, whereas three had delayed surgical treatment due to clinical deterioration despite conservative therapy. The indications for surgery were clinical and radiological evidence of transmural infarction in six cases, three of whom showed additional sign of colon perforation, profuse bleeding in one case and in one case colon resection was performed due to incidental finding of gangrenous colon during surgery for other medical reasons. Colonic resection was performed in all surgical patients, four patients had segmental resection (left hemicolectomy in one case, transversectomy in one case, right hemiocolectomy in two cases), while subtotal/total colectomy was carried out in the other four patients. Primary anastomosis was only performed in one patient, while stoma was created in the remaining seven patients, one of whom had their stoma subsequently closed. One patient underwent second look surgery, but no additional resection was required. All of the 13 patients who experienced recurrence during the study period had previously been treated with conservative management during their initial episode. Likewise, they were all managed conservatively at relapse. Still, surgery was indicated for one of these patients, but the patient was not considered a surgical candidate due to poor physical condition and old age.

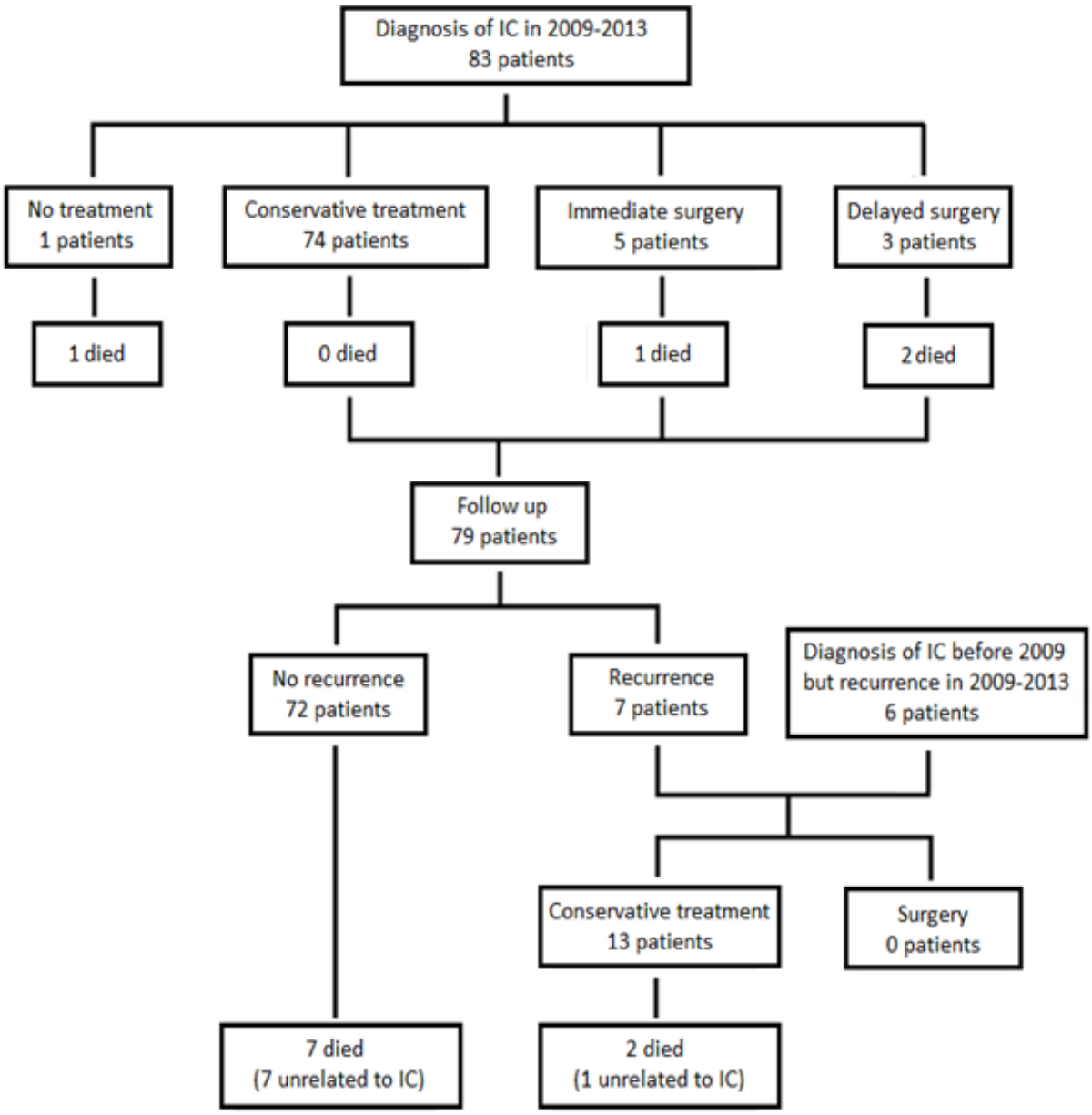

Figure 9 Flow chart depicting management and immediate and long-term clinical outcome of patients diagnosed with ischemic colitis in 2009-2013. Six patients who had a recurrent ischemic colitis in 2009-2013 but were initially diagnosed with ischemic colitis prior to the study period were included in statistical analyses.

4.8 Immediate Clinical Outcome

All conservatively treated patients, except one, had an uneventful clinical course. This patient, died during a recurrent episode of ischemic colitis. The patient had signs of severe disease, evidenced by presence of abdominal distention, but was not considered a suitable surgical candidate, as mentioned before. Three of the surgically managed patients died postoperatively, two of whom had delayed surgical intervention. One patient passed away prior to receiving medical care and was diagnosed with ischemic colitis at autopsy. The overall in-hospital mortality rate was 6%. The mean length of hospitalization for the surviving conservatively treated patients was 6 days (± 5), while the surviving surgically managed patients had a mean length of 128 days (± 15). The mean survival of patients who died postoperatively was 30 days (± 14).

Ten (11%) patients had poor outcome including five patients who underwent surgery and survived, three patients who underwent surgery and died and two patients who died without any surgical intervention. All cases, but one, were observed during the initial episode (Figure 9). The results of univariate analysis of predictive factors for poor outcome are shown in Table 5. Four factors were found to predict poor outcome with statistical significance in univariate analysis: absence of hematochezia, shock, tachycardia and location of ischemia. The two groups were also compared with regard to independent cardiovascular diseases and laboratory investigations, but no differences were found with statistical significance (data not shown). The results of multivariate analysis of predictive factors for poor outcome are shown in Table 6. In the multivariate analysis, two factors were found to predict poor outcome with statistical significance: location of ischemia in the right colon and simultaneous involvement of both the left and right colon, in both instances relative to left-sided ischemia.

Table 5 Results of univariate analysis of predictive factors for poor outcome (surgery and/or in-hospital death).

	Favorable outcome (n=79)	**Poor outcome (n=10)**	**p-value**
Age (years)	64 (±18)	73 (±13)	0.1302
Female/Male	53/26	8/2	0.4954
History of smoking habit[1]	47 (60)	8 (80)	0.3064
Comorbidities[2]			
Cardiovascular disease	55 (70)	7 (70)	1.0000
HT	48 (61)	7 (70)	0.7356
IHD	17 (22)	2 (20)	1.0000
AF	10 (13)	1 (10)	1.0000
HF	6 (8)	0 (0)	1.0000
CVD	6 (8)	2 (20)	0.2202
PAD	4 (5)	1 (10)	0.4570
Diabetes mellitus	5 (6)	2 (20)	0.1759
Chronic renal failure	4 (5)	1 (10)	0.4570
History of cancer	12 (15)	0 (0)	0.3462
Hypercholesterolemia	24 (30)	2 (20)	0.7171
COPD	9 (11)	4 (40)	0.1032
Comorbidities[3]	61 (77)	8 (80)	1.0000
Clinical presentation			
Abdominal pain	73 (92)	10 (100)	1.0000
Hematochezia	**76 (96)**	**4 (40)**	**<0.0001**
w/significant bleeding	11 (14)	3 (30)	0.1893
Diarrhea	60 (76)	6 (60)	0.2756
Shock	**0 (0)**	**2 (20)**	**0.0115**
Tachycardia	**29 (37)**	**8 (80)**	**0.0131**
Abdominal tenderness	71 (90)	9 (90)	1.0000
Location of disease			
Only left colon	**75 (95)**	**3 (30)**	**<0.0001**
Only right colon	**2 (3)**	**3 (30)**	**0.0093**
Both left and right	**2 (3)**	**4 (40)**	**0.0011**

[1] Unknown smoking habit in 10 cases (11. 2%).
[2] HT, hypertension; IHD, ischemic heart disease; AF, atrial fibrillation; HF, heart failure; CVD, cerebrovascular disease; PAD, peripheral arterial disease.
[3] Patients who have at least one of the comorbitites listed above.

Table 6 Results of multivariate analysis of predictive factors for outcome (surgery and/or in-hospital death).

	Odds ratio	95 % CI[1]	p-value
Only right colon	37.50	4.70-392.85	0.0009
Both right and left colon	50.00	7.16-499.39	0.0002

[1] CI, confidence interval.

4.9 Long-Term Clinical Outcome

Data regarding long-term outcome of the 79 patients (95%) who survived the initial episode of ischemic colitis were recorded over a mean follow-up period of 24 months (range, 0-63 months). During this period, seven patients (9%) experienced recurrence of ischemic colitis. Additionally, six patients who were diagnosed with ischemic colitis prior to the study period had a recurrent episode of the disease between 2009 and 2013. These patients were included in the analysis of recurrence (Figure 9). The mean time interval between episodes was 2.2 years (± 1.8). The results of univariate analysis of predictive factors for recurrence are shown in Table 7. Two factors were found to predict recurrence with statistical significance: presence of at least one of the investigated comorbidities in the current study and absence of abdominal tenderness at hospital admission. The two groups were also compared with regard to laboratory investigation, form and location of disease as well as management, but no differences were found with statistical significance (data not shown). The results of multivariate analysis of predictive factors for recurrence are shown in Table 8. In the multivariate analysis, two factors were found to predict recurrence with statistical significance: hypertension and absence of abdominal tenderness at hospital admission.

During the follow-up, several patients had subsequent non-gastrointestinal vascular events. Two patients experienced myocardial infarction, one had cerebrovascular event and one developed peripheral arterial disease. At the end of the study period, 13 patients (15%) had died (Figure 9). Five patients (6%) died from sepsis and multiple organ failure as a result of ischemic colitis, in four cases during the initial episode but in one case at relapse. The remainder had alternative causes of death: five patients (6%) died from metastatic lung cancer, one (1%) died from liver cirrhosis, and three (3%) died of unknown cause. The mortality rate was significantly higher among those who underwent surgery (n=5, 63%) than those who did not (n=8, 10%) (p=0.0014). The overall survival rate was 85%, while the survival rate for patients who recovered from ischemic colitis was 90%.

Table 7 Results of univariate analysis of predictive factors for recurrence.

	No recurrence (n = 67)	**Recurrence (n = 13)**	**p-value**
Age (yr)	63 (±18)	71 (±10)	0.1282
Female/Male	44/23	10/3	0.5305
History of smoking habit[1]	48 (72)	7 (54)	0.3260
Comorbidities[2]			
Cardiovascular disease	44 (66)	12 (92)	0.0948
HT	38 (57)	11 (85)	0.0694
IHD	13 (19)	4 (31)	0.4585
AF	9 (13)	1 (8)	1.0000
HF	4 (6)	2 (15)	0.2501
CVD	4 (6)	2 (15)	0.2501
PAD	2 (3)	2 (15)	0.1216
Diabetes mellitus	3 (4)	3 (23)	0.0511
Chronic renal failure	3 (4)	2 (15)	0.1838
History of cancer	8 (12)	4 (31)	0.0991
Hypercholesterolemia	21 (31)	3 (23)	0.7445
COPD	7 (10)	2 (15)	0.6344
Comorbidities[3]	**49 (73)**	**13 (100)**	**<0.0001**
Clinical presentation			
Abdominal pain	62 (93)	13 (100)	0.5855
Hematochezia	65 (97)	12 (92)	0.4169
w/ significant bleeding	9 (13)	1 (8)	1.0000
Diarrhea	51 (76)	12 (92)	0.2797
Tachycardia	20 (30)	5 (38)	0.5313
Fever	4 (6)	2 (15)	0.2501
Abdominal tenderness	**63 (94)**	**7 (54)**	**0.0018**

[1] Unknown smoking habit in 10 cases (11. 2%).
[2] HT, hypertension; IHD, ischemic heart disease; AF, atrial fibrillation; HF, heart failure; CVD, cerebrovascular disease; PAD, peripheral arterial disease.
[3] Patients who have at least one of the comorbitites listed above.

Table 8 Results of multivariate analysis of predictive factors for recurrence.

	Odds ratio	**95 % CI[1]**	**p-value**
Hypertension	6.9	1.3-68.2	0.0472
Abdominal tenderness	0.085	0.006-0.254	0.0008

[1] CI, confidence interval.

5 Discussion

5.1 Incidence

To date, few studies have investigated the incidence rate of ischemic colitis in the general population. To our knowledge, only four population-based studies have addressed this topic and none of them have been published in a full-manuscript form. Three of these studies reported an incidence rate that ranged from 4.5-9.9 cases per 100.000 persons/year, while the fourth described an incidence rate of 44 cases per 100.000 persons/year for persons 40 years or older (11). The current study demonstrated a mean incidence rate of 7.3 cases per 100.000 persons/year for persons 18 years or older, which is consistent with findings of three of the previously mentioned studies. However, due to a strict case definition of ischemic colitis in the present study, it is likely that the true incidence rate is higher. Histological confirmation of ischemic colitis was required for participation, but some diagnoses of ischemic colitis are indeed established without a biopsy sampling (106, 116). Likewise, the disease is reported to be frequently mis- or underdiagnosed because healthcares' level of suspicion is often low and the symptoms are frequently self-limiting and nonspecific. This provides yet another reason to believe that the incidence might be underestimated. Another contributing factor that might have limited the study's estimated incidence rate resides in the identification of cases, which is largely based on appropriate coding for this unusual disease. However, to minimize the impact of this, an advanced search was conducted that should have covered the majority, if not all, cases of ischemic colitis that required medical attention. In addition to search for ICD-10 codes compatible with ischemic colitis in the diagnosis database, a search for the term "ischemic colitis" in the text of electronic medical records was undertaken and the database of the pathological department was screened for histological diagnosis of ischemia in the colon.

In accordance with previous studies, the results of the current study demonstrate that the incidence of ischemic colitis increases substantially with age (11). The incidence rate for the oldest age group, which consisted of 90-99 year old individuals, turned out to be 38.3 cases per 100.000 persons/year. This is well above the observed mean incidence rate of the entire study population and further emphasizes that ischemic colitis is primarily disease of the elderly. Nevertheless, ischemic colitis affected young adults as well. A total of sixteen patients were younger than 50 years of age and the disease was even diagnosed in individuals as young as 20 years of age. This broad age range is likely attributable to different clinical background as the etiology of ischemic colitis is extremely diverse. In older individuals the cause is presumably multifactorial, while in younger patients, the etiology is considered to be more specific. Differences between patients of different age group have been investigated to

some extent. Kimura et al. found smoking habit and hyperuricemia to be more common in young adults with ischemic colitis, while the prevalence of accompanying conventional risk factors, such as hypertension, was low among the younger patients (107).

Furthermore, the study revealed that ischemic colitis is markedly more prevalent among females than males. Previous studies have demonstrated the same trend (11, 20). However, this is not constant across the literature as some studies have revealed the opposite (21). Nevertheless, large-scale studies, which have more statistical power to draw conclusion about gender distribution, have all demonstrated a female predominance of ischemic colitis (11). The reasons for these gender differences have not been established yet. It might be attributable to common use of oral contraceptive pills or hormonal replacement therapy among females, but both of these medications have been associated with ischemic colitis (54). Also, irritable bowel syndrome and constipation are more frequent among females than males (108), and studies have shown that patients with irritable bowel syndrome and constipation have a two- to three-fold increased risk for ischemic colitis (70). The gender distribution and differences of patients with ischemic colitis requires further research, but insofar, no study has set out to examine variations between female and male patients with ischemic colitis.

Also, in the present study, male patients were found to be significantly younger than the female patients. This might be associated with the fact, that cardiovascular diseases, well-known risk factors for ischemic colitis, develop 10 years later in females than in males due to protective effects of estrogen in females prior to menopause (109). Also, this difference might be attributable to cocaine and methamphetamine abuse, another well-known risk factor for ischemic colitis, but illicit drug abuse has been shown to be highest among young men (110).

5.2 Risk Factors

It is important to consider conventional risk factors for ischemic colitis when patients are being evaluated for the disease. Various medical conditions and pharmacological agents have been associated with ischemic colitis (32). Supporting previous findings, the present study showed that cardiovascular risk factors and major cardiovascular conditions are frequent among patients with ischemic colitis (13). Reported in 62% of the patients, hypertension was by far the most common comorbidity. The study further revealed that hypercholesterolemia, ischemic heart disease, atrial fibrillation, cerebrovascular disease and diabetes mellitus are all common comorbidities among patients with ischemic colitis. Overall, a total of 70% of the patients had a history of some kind of cardiovascular condition. Additionally, many patients had pre-existing chronic obstructive pulmonary disease and a history of cancer. Previous

studies have described a connection between chronic obstructive pulmonary disease and ischemic colitis (11). This relationship might be linked to direct effects of hypoxemia associated with chronic obstructive pulmonary disease or reflect an underlying small vessel disease from long-term exposure to cigarette smoking. Likewise, a history of cancer might reflect the effects of chemotherapeutic agents, but several studies have reported ischemic colitis in conjunction with administration of such agents (61). However, direct influence of cancer in the pathogenesis of ischemic colitis has not been demonstrated. Detailed evaluation on the history of cancer in patients of the current study, regarding cancer type and therapeutic approaches, did not reveal any obvious associations. These connections warrant further research.

Interestingly, nearly two-thirds of the study population were active cigarette smokers or had a history of smoking. This number might be even higher, as data on smoking habit were not documented in 9% of cases. According to data from the Directorate of Health in Iceland, a total of 18.4% of Icelanders were active smokers during the period of 2009-2012 and 34.0% were ex-smokers. Data were not available for the year of 2013. Although not an ideal control group, this suggests that smoking habit is more frequently seen among patients with ischemic colitis than in the general population. Nevertheless, to truly determine the importance of cigarette smoking in the development of ischemic colitis, a further research with matched controls is needed.

As mentioned before, Kimura et al. described a relationship between cigarette smoking and occurrence of ischemic colitis in young adults, but other than that little data exist on the role of smoking in the pathogenesis of ischemic colitis (107). Kimura et al. proposed that cigarette smoke might predispose to colon ischemia due to its pro-atherogenic properties, hypercoagulative effects and vasospasmic influences. Cigarette smoke has been shown to decrease nitric oxide bioactivity and induce oxidative stress generation due to stimulation of NADPH oxidase, in turn impairing endothelial function and promoting atherosclerosis (111). Also, cigarette smoke may promote hypercoagulation by its influences on platelet adhesiveness and hemorheology (112). Finally, it has been demonstrated that cigarette smoke may increase endothelial sensitivity and therefore increase susceptibility to vasoconstriction (113). Supporting this, cigarette smoke has been shown to suppress acetylcholine-induced endothelium-dependent vasodilation in animal models (114). Although these are all plausible mechanism, they require further research in context with ischemic colitis.

A total of 8% of the patients had none of the comorbidities investigated in the current study nor history of smoking. The pathogenesis of ischemic colitis in some of these patients

might be related to pharmacological agents, but speculations on such connections cannot be made as medications and illicit drug abuse among the study population was not investigated due to limitations of the retrospective study design.

5.3 Clinical Manifestations

The clinical presentations found in the current study were quite similar to those observed in previous studies (20, 22). The initial symptoms generally comprise acute abdominal pain, hematochezia and diarrhea, regardless of disease severity. Most patients in the current study presented with all three of these symptoms, still, approximately one-third of the patients had only one or two of them. As a consequence, even though patients only present with part of the aforementioned symptoms, clinicians should always bear in mind the possibility of ischemic colitis, especially if patients have conventional risk factors for ischemic colitis such as history of cardiovascular disease or if they have otherwise clinical suspicion of ischemic colitis.

The left colon, particularly the splenic flexure, has been reported to be the most frequently affected site in ischemic colitis (31). However, involvement of the right colon is being reported with increasing frequency (21, 33). In the present study, the left colon was the primary site of involvement, whereas only five patients had isolated right-sided colon involvement. The prevalence of isolated right-sided colon involvement in the current study was considerably low in comparison with previous studies. This might be due to differences in case definitions (9, 106). In the current study, all patients with thromboembolic event in the SMA were excluded, but occlusion of this artery may result in ischemic injury isolated to the right colon as part of acute mesenteric ischemia (16). Additionally, the study demonstrated that involvement of all parts of the colon is not uncommon. Six patients had ischemia located in both the right and left colon to some extent and three of those six patients had diffuse involvement of the entire colon. Although the pathophysiology behind such extensive disease has not been described in detail, this atypical distribution is likely the result of low-flow state with secondary vascular constriction, rather than vascular occlusion, as that would more likely result in segmental colon involvement. The current study's data support this thesis, as two of the patients, who had diffuse involvement, presented with shock at admission. The third patient had concomitant pancreatitis.

5.4 Outcome

A major focus of the current study was to analyze the outcome of patients with ischemic colitis. Fortunately, majority of the patients had a mild disease of transient nature that could be managed successfully without operation. However, a total of ten patients underwent

surgery and/or died during hospitalization for ischemic colitis. In the medical literature the overall prognosis of patients with ischemic colitis is considered to be good, but it has been estimated that approximately 20% of patients with ischemic colitis will require surgery (16). Compared with previous studies, the numbers of severe cases in the present study are relatively low, with only 10% of the patient having required surgical intervention. This difference is probably due to variations in case definition. In the current study colon ischemia in relation to vascular surgery and thromboembolic event in the SMA and IMA was excluded, but both of these conditions have been associated with a severe presentation of the disease (115). Also, the observed differences in numbers of severe cases across studies might be related with the fact that this was a population-based study. In studies from tertiary referral centers, patients who are more critically ill are presumably over represented.

Patients' prognosis resides largely on a high index of suspicion and prompt diagnosis followed by appropriate treatment. Despite advances in surgical techniques and intensive care the operative mortality rate for ischemic colitis remains high. The overall operative mortality rate in the current study was 38% which is in line with previous study findings (8, 106). Furthermore, the present study demonstrates a higher mortality rate for those who have delay in surgical intervention. For patients who underwent immediate surgery the operative mortality rate was 20%, while it was found to be considerably higher, or 67%, for those who had delayed surgery. This calls into question whether patients who had surgery later on should have been operated on earlier. However, none of these patients had indication for emergency surgery according to guidelines as they lacked signs of peritonitis at presentation and radiological studies revealed no signs of colon infarction. It was not until later in the course of the disease, that the patients were considered to be surgical candidates. It is therefore important to identify factors that predict severe outcome so healthcares can be more alert if patients are expected to have poor outcome, as rapid recognition and resection can prove to be fundamental for survival in more severe cases of ischemic colitis.

In the current study, multivariate analysis revealed two independent factors predictive of poor outcome. They were location of ischemia in the right colon alone and simultaneous involvement of both the left and right colon, in both instances relative to ischemia confined to the left colon. This is in accordance with previous studies but unfavorable outcome in patients diagnosed with ischemic colitis has been investigated quite extensively. Majority of these previous studies, as the current study, found involvement of the right colon to be related to a more severe presentation of the disease (9, 10, 103). The present study further demonstrated a concomitantly involvement of the left colon as an independent predictor of adverse outcome.

Of all the ten patients with severe presentation of ischemic colitis in the current study, three had isolated right-sided colitis and four had simultaneous involvement of the right and left colon. The pathogenesis behind ischemic involvement of the right colon has not been explained in detail. Still, it has been implicated with vasoconstriction of the highly sensitive vasa recta due to repeated hypotensive episodes. These conditions are considered to primarily affect the right colon as the vasa recta in the right colon have been found smaller and less developed as compared to those in the left colon. Also, the vasa recta of the right colon are longer and originate further away from the bowel than those on the left side (103). As a consequence, resistance to reperfusion after an episode of hypotension is higher in the vasa recta of the right colon. In accordance with this hypothesis, previous studies have also described a higher prevalence of right-sided colitis and poor outcome in patients with chronic renal failure, especially those on hemodialysis, as such condition frequently cause perturbation in blood flow (103). Still, the current study was not able to demonstrate this relationship. Of all the 89 patients included in the study, only five patients had chronic renal failure and only one of them had poor outcome. Also, none of these patients were on hemodialysis and none had right-sided colitis. Previous studies, aimed at assessing predictors of severe outcome, have not all been able to demonstrate significant connection between renal failure and severe outcome like the current study, which is why this warrants further research (8). Moreover, several studies have found a linkage between clinical presentation without hematochezia and severe outcome (8). The present study detected a significant linkage between these factors in univariate analysis, but was not able to demonstrate it in multivariate analysis. The same applies to initial hemodynamic instability and tachycardia at hospital admission (21, 116).

Several patients in the current study developed chronic gastrointestinal symptoms following their initial episode of ischemic colitis. It has been estimated that about 15% of patients develop strictures (32). Yet, no patient in the present study subsequently developed symptomatic stricture. In the current study, thirteen patients had experience of recurrent ischemic colitis, six of whom had previously been diagnosed with the disease prior to the study period. This accounts for a five-year recurrence rate of 9%, which is slightly lower as compared with previous studies which have mostly reported a five-year recurrence rate ranging from 10% to 16% (22, 106). Research on recurrent ischemic colitis is largely lacking and very few studies have assessed factors predictive of recurrence.

The very few studies which have assessed predictors of recurrence, findings have not been consistent. Mosli et al. found coronary artery diseases and elevated serum creatinine to

be predictive of recurrent ischemic colitis (20), while another study demonstrated that acute abdominal pain, vomiting and location of sigmoid colon were predictive of recurrence (117). The current study revealed two independent factors predictive of recurrence with statistical significance. These were hypertension and absence of abdominal tenderness at initial hospital admission. Hypertension is a well-established cardiovascular risk factor that may contribute to ischemic colitis. Its connection with recurrence is presumably a reflection of a generalized atherosclerotic disease that may compromise blood flow to the colon and thus render the colon more susceptible to other precipitating events. In regard to the predictive influence of an absent abdominal tenderness on recurrence, caution must be taken in the interpretation. As opposed to diagnosis of hypertension, the presence of abdominal tenderness is not entirely definite. The experience of abdominal tenderness might differ between individuals, and the recording of this finding in medical records might not be consistent, as it is quite nonspecific. Besides that, a logical pathophysiological mechanism that might explain this linkage could not be detected by the author of this thesis. This connection has not been demonstrated before and requires further research. None of the other investigated factors in the current study were found predictive of recurrence with statistical significance. Nevertheless, one might consider several of these factors to have a borderline statistical significance in the univariate analysis. They include a co-existing cardiovascular disease, diabetes mellitus and history of cancer. Although, it is not possible to draw any firm conclusions regarding these factors based on the current study's data, an evaluation in the future with a larger cohort might provide better insight on the impact of these factors on recurrence.

Despite the advanced age of the study population and various comorbidities, the long-term prognosis was fairly good. After a mean follow-up of 2 years, the overall mortality rate was 15%. Five patients died due to ischemic colitis and eight had alternative causes of death. Findings of the current study indicate that the prognosis of patients who undergo surgery is generally unfavorable whereas those who can be managed conservatively usually have good long-term prognosis. This is presumably because those who require surgical intervention are more critically ill and demonstrate a more severe form of the disease than those who can be managed conservatively.

5.5 Limitations and Advantages

The main advantage of the current study is that it only includes patients who have histologically confirmed diagnosis of ischemic colitis. This unambiguous diagnosis of the disease ensures that no patient with misdiagnosis of ischemic colitis is included in the study.

This is important, as the clinical, biochemical, radiological and endoscopic findings for ischemic colitis are all relatively unspecific, and thus the disease can only truly be confirmed by histological assessment. Another advantage of the present study resides in the extensive search in the hospital's databases. This advanced search was done to enable a complete identification of all patients with ischemic colitis. This is especially important as there is no specific ICD-10 code designated for ischemic colitis, so the accuracy of appropriate diagnostic coding for ischemic colitis is not very high.

The main limitation of the current study is the retrospective design. Although variables are collected from medical records that are designed to provide concise description of patients' clinical history and lifestyle habits, it is possible that some of the investigated variables are underreported. Additionally, being a retrospective analysis, conditions and factors implicated with the development of ischemic colitis, such as physical activity prior to admission, history of constipation and administration of various medications, could not be evaluated. Another of the present study's limitation is the low statistical power due to small sample sizes of patients with poor outcome or recurrent ischemic colitis. As a consequence, the identified predictors of poor outcome and recurrence in the study's statistical analyses might be secondary to the small sample size and all connections demonstrated in these analyses must therefore be interpreted with caution. Yet another limitation of the current study is the lack of matched control group. This made it impossible to predict the impact of implicated risk factors for ischemic colitis such as influences of cigarette smoking.

5.6 Future Directions

The results presented in the current study suggest that isolated right-sided colitis and simultaneous involvement of the right and left colon are predictive of poor outcome and that those diagnosed with hypertension and presented with no abdominal tenderness are likely to experience a recurrent ischemic colitis. However, due to small sample size these connections must be interpreted with caution. An ongoing research with an associated larger sample size would give a more reliable estimate of these associations. Furthermore, a prospective study with matched controls is greatly needed in order to evaluate the impact of all implicated risk factors of ischemic colitis such as physical activity, coagulation defects, constipation, various medication and illicit drug abuse. To our knowledge, no such study has ever been conducted but it would provide invaluable insight to the nature and causes of this unusual disease.

Conclusion

In conclusion, the incidence of ischemic colitis in Iceland is approximately 7.3 cases per 100.000 inhabitants, 18 years and older, per year. The disease is more prevalent in elderly patients and females. Most patients present with abdominal pain, diarrhea and hematochezia, but few have clinical significant bleeding. The left colon is the predominant location of ischemic colitis but isolated right-sided colitis or simultaneous involvement of the right and left colon are predictive of poor outcome. Patients presented with ischemia confined to these colon areas should therefore be more carefully observed and managed, as prompt diagnosis and resection can prove to be lifesaving in cases of severe ischemia. Approximately 9% of patients required surgical intervention and prognosis of those individuals was generally unfavorable whereas those who could be managed conservatively had a good long-term prognosis. In a population-based setting approximately 9% of the patients experienced a recurrent ischemic colitis. Multivariate analysis demonstrated that patients diagnosed with hypertension and present with no abdominal tenderness are more likely to relapse. The high prevalence of smoking habit among patients with ischemic colitis warrants further research.

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