Family History as Predictor of Recurrent Diverticulitis After an Episode of Uncomplicated Diverticulitis

Turki Almalki, # 260794665, McGill University, Montreal

15th August 2019

A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of Master of Science, Experimental Surgery

Table of contents

Abstract

In recent years, management strategies for diverticulitis have evolved in response to increasing evidence to support more conservative treatment approaches. Due to this shift in increased non-operative management, recurrent diverticulitis has become a significant problem. Though not all patients will develop a recurrence, up to 35% may experience at least one more episode of the disease. There is uncertainty and inconsistency regarding the predictors of recurrent diverticulitis, which has led to challenges in clinical decision making. Several retrospective analyses reported on the predictors of recurrence of acute diverticulitis but only one study reported on the impact of family history on the risk of recurrence. To address this gap, we investigated the role of family history on the risk of diverticulitis recurrence. We observed a strong impact of family history on the risk of diverticulitis recurrence. Furthermore, we found that the number of relatives has a specific role. Finally, we observed a significant impact of family history on the risk of a complicated recurrence. These findings can guide future decision making when considering risk factors for recurrence and the role of elective colectomy.

Résumé

Ces dernières années, les stratégies de gestion de la diverticulite ont évolué grâce aux données plus probantes en faveur de traitements plus conservatrices. En raison de ce changement dans la gestion non-opératoire accrue, la diverticulite récurrente est devenue un problème important. Bien que tous les patients ne développent pas de recurrence, jusqu'à 35% d'entre eux peuvent subir au moins un autre épisode de la maladie. Les prédictions de la diverticulite récurrente sont peu fiables et inconsistents, ce qui a rendu la prise de décision clinique difficile. Plusieurs analyses rétrospectives ont rapporté certains facteurs prédicteurs de la réapparition de la diverticulite aiguë, mais une seule étude s'est intéressé à l'impact des antécédents familiaux sur le risque de récurrence. Pour combler cette lacune, nous avons étudié le rôle des antécédents familiaux sur le risque de recurrence de la diverticulite. Nous avons observé un fort impact des antécédents familiaux sur le risque de recurrence de diverticulite. De plus, le nombre Membres de la famille joue un rôle spécifique. Enfin, nous avons observé un impact significatif des antécédents familiaux sur le risque de récurrence compliquée. Ces résultats peuvent guider les décisions futures lors de la prise en compte des facteurs de risque de recurrence et du rôle de la colectomie élective.

Acknowledgments

Foremost, I would like to express my sincerest gratitude to my supervisor Dr. Marylise Boutros for her ongoing support, guidance, enthusiasm, patience, and immense knowledge. I could not ask for a better mentor to learn from, both as a surgeon and as a researcher.
I would like to thank the members of my thesis committee: Dr. Geraldine, Dr. Liberman, and Dr. Bergman for their guidance throughout this project. I am grateful to my talented colleagues Richard Garfinkle, Sarah Sabboobeh, Georgia Rigas, Marie Demian for their help and collaboration in this project.

I would like to thank my sponsor Prince Sattam Abdulaziz University and Saudi Arabian Cultural bureau (SACB) for their continuous support and funding my scholarship studying.
Finally, I would like to thank my family - words cannot express the gratitude I feel for their ongoing love and encouragement. And to my Dad and Mom - thanks for being the first to show me what it means to be a dedicated scientist. And to my Brother Hani and my lovely sisters (Bashear, Mashael and Shatha)- for being supportive through my entire journey. And to my partner Marwah- Thanks for being supportive, thoughtful and fulfilling my life.

Author contributions

Manuscript (Chapter 2): Family History is Associated with Recurrent Diverticulitis After an Episode of Diverticulitis Managed Non-Operatively

1. **Almalki, T.**: Substantial contributions to the conception and design of the work; acquisition, analysis, and interpretation of data for the work; AND co-primary author of the work, revised it critically for important intellectual content; AND will give final approval of the version to be published; AND agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved
2. **Garfinkle, R.**: Substantial contributions to the conception and design of the work; acquisition, analysis, and interpretation of data for the work; AND co-primary author of the work, revised it critically for important intellectual content; AND will give final approval of the version to be published; AND agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved
3. **Kmiotek, E.**: Substantial contributions to the conception and design of the work; acquisition, analysis, and interpretation of data for the work; AND revised it critically for important intellectual content; AND will give final approval of the version to be published; AND agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved
4. **Pelsser, V.**: Substantial contributions to the conception and design of the work; acquisition, analysis, and interpretation of data for the work (radiological review); AND revised it critically for important intellectual content; AND will give final approval of the version to be published; AND agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved
5. **Bonaffini, P.**: Substantial contributions to the conception and design of the work; acquisition, analysis, and interpretation of data for the work (radiological review); AND revised it critically for important intellectual content; AND will give final approval of the version to be published; AND agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved
6. **Reinhold, C.**: Substantial contributions to the conception and design of the work; acquisition, analysis, and interpretation of data for the work (radiological review); AND revised it critically for important intellectual content; AND will give final approval of the version to be published; AND agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved
7. **Yousef, P.**: Substantial contributions to the conception and design of the work; acquisition, analysis, and interpretation of data for the work; AND revised it critically for important intellectual content; AND will give final approval of the version to be published; AND agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

8. **Morin, N.**: Substantial contributions to the conception and design of the work; acquisition, analysis, and interpretation of data for the work; AND revised it critically for important intellectual content; AND will give final approval of the version to be published; AND agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved
9. **Vasilevsky, C.A.**: Substantial contributions to the conception and design of the work; acquisition, analysis, and interpretation of data for the work; AND revised it critically for important intellectual content; AND will give final approval of the version to be published; AND agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved
10. **Liberman, S.**: Substantial contributions to the conception and design of the work; acquisition, analysis, and interpretation of data for the work; AND revised it critically for important intellectual content; AND will give final approval of the version to be published; AND agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved
11. **Boutros, M.**: Substantial contributions to the conception and design of the work; acquisition, analysis, and interpretation of data for the work; AND senior author of the work, revised it critically for important intellectual content; AND will give final approval of the version to be published; AND agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Journal Submission:
Manuscript (Chapter 2): Family History is Associated with Recurrent Diverticulitis After an Episode of Diverticulitis Managed Non-Operatively is submitted to peer reviewed journal "The Diseases of the Colon & Rectum (DCR)". It is currently under process of revision and consideration for publication.

Chapter1:Background and Objectives

Epidemiology and Incidence of Diverticulitis

Diverticular disease is estimated to be present in more than 65% of patients over the age of 65. About 20% of patients with diverticular disease who develop diverticulosis are younger than the age of 50 (1, 2). Diverticular disease of the colon is very common in Western countries and has significant impact on patient health as well as increasing the burden of health care costs (1, 2). Historically, it has been known that almost 15% of patients diagnosed with diverticulosis progress to diverticulitis during their lifetime (4, 5). However, this finding is not backed up by population-based studies, thus giving an inaccurate overestimation of the actual risk. Recent studies have reported that the true risk of diverticulitis is <5% of those who have colonic diverticulosis (5). A nationwide inpatient sample (NIS) study in the United States reported an increase of 26% in acute diverticulitis admissions between 1998 and 2005 (6) with a high incidence of acute diverticulitis in patients between the ages of 18 and 44 years (82%). The study also found that the mean age for admitted patients decreased from 64.6 to 61.8 years. Another study using data from NIS for the years 2002 to 2011 showed that the mean age at admission had significantly decreased from 61.9 in 2002 to 60.5 years in 2011 (7). These number indicated that the cost burden of this disease is increasing significantly on both patients and healthcare resources over the time. For Example, In the United States, the annual cost of diverticulitis treatment is estimated to be over 2 billion dollars per year (6).

Pathophysiology of diverticular disease and diverticulitis

Pathophysiology of diverticulosis

Diverticula develop at points of weakness in the colon, where the vasa recta capillaries penetrate the circular smooth muscle layer in the colonic wall (8). These colonic diverticula are considered false diverticula as they only contain outpouchings of the mucosa and submucosa. Currently, the exact process of diverticula formation is not completely understood. It was previously thought that diverticula formation is a result of increased pressure in weakened areas of the colonic wall, particularly in the aging population. More recent theories, however, have spurred research into different potential factors implicated in the development of diverticula, such as colonic motility, genetics, inflammation, and the microbiome.

Supporting the hypothesis of an etiology based in colonic motility, the myenteric plexus, myenteric glial cells, and interstitial cells of Cajal are affected by neural degeneration. Patients with diverticulosis have exaggerated and uncoordinated contractions due to loss of neurons that lead to elevated intraluminal pressure, eventually causing herniation of the mucosa and submucosa. Some studies have further reported that an upregulation of mucosal neuropeptides, such as serotonin and acetylcholine, coupled with mucosal inflammation, contribute to abnormal colonic motility, thus leading to diverticula formation (9-11).

Further studies have shown that development of diverticular disease can be attributed to genetics. For example, some connective tissue disorders with genetic predispositions, such as Ehlers–Danlos's disease, Marfan's syndrome and polycystic kidney disease, may affect the structural changes in the wall, leading to the development of diverticula at an early age (12, 13).

Notably, a Swedish Twin database of 104,450 twins reported diverticular disease in 2296 twins. The study reported an odds of diverticular disease development for monozygotic and dizygotic

twins to be 7.15 (95% CI 4.82–10.61) and 3.20 (95% CI 2.21–4.63),respectively (14). However, the evidence that links genetics with diverticular development is sparse.

Pathophysiology of diverticulitis

The mechanism of progression from diverticulosis to diverticulitis is not clearly understood. Diverticulitis arises from inflammation affecting the diverticula and is accompanied by macro- or microscopic perforations. One common theory is that obstruction of the diverticulum with stool leads to microbial overgrowth and ischemia of the local tissue, which eventually lead to perforation(4, 5). Another, more recent, theory postulates that changes in the microbiome may be implicated in the development of diverticulitis. Long-standing fecal stasis can lead to an imbalance of the microbiome , which may in turn lead to a chronic inflammatory condition (4). In one study, it was found that patients with diverticulitis have a higher diversity in fecal microbiota than control patients. (15).

Diagnosis of diverticulitis and classification

Clinical presentation and physical examination:

Acute diverticulitis has different clinical presentations depending on the severity and complications of the inflammatory process. One of the most common complaints in patients presenting with diverticulitis is abdominal pain, which typically has an acute to subacute onset (16). The pain usually starts in the lower left quadrant due to the location of the sigmoid and descending colon (left-sided diverticulitis) (17). However, patients might report pain in the suprapubic area because of the redundant and mobile nature of the inflamed sigmoid colon. (18). The nature of the pain is usually dull and constant. About 50% of patients report previous episodes of similar pain that were undiagnosed (19, 20). In more severe cases of diverticulitis, nausea and vomiting may occur due to a bowel obstruction or ileus from peritoneal irritation (20). Patients may also experience low-grade fever. Circulatory shock with hypotension is uncommon but can be a presentation of diverticulitis with frank perforation and peritonitis. This presentation is considered a complicated case of diverticulitis.

Patients with acute diverticulitis also report changes in bowel habits: 50% of patients reported obstipation while 25% to 35% reported diarrhea (21). At the time of presentation, approximately 25% of patients with diverticulitis could potentially develop acute or chronic complications (22). Complications include abscess, perforation, obstruction, and fistula. Around 17% of patients admitted with acute diverticulitis appear to have diverticular abscesses (23). A diverticular abscess can be seen on abdominal computed tomography (CT) scan upon initial presentation or may subsequently develop after the first episode.

Perforation with peritonitis occurs in 2% of patients with diverticulitis. It may occur as a result of a diverticular abscess rupturing into the peritoneal cavity or alternatively free rupture of an inflamed diverticulum with fecal peritonitis (24-26). Mortality rates reach up to 20% in patients with perforation (24-26).

Laboratory findings: Patients with acute diverticulitis are commonly found to have a mildly elevated white blood cell (WBC) count and high levels of C-reactive protein (CRP) levels. Normal white blood cell count can be observed with mild diverticulitis and have been reported in up to 45% of patients with acute uncomplicated diverticulitis (27). CRP elevation could be found in severe diverticulitis and complicated cases. In one prospective study, it was found that CRP levels >173 mg/L, collected at the time of the initial assessment, in the Emergency Department could help predict the onset of complicated diverticulitis. Such patients commonly need emergency surgery for peritonitis or percutaneous drainage of an abscess(28).

Radiological Investigations: Diverticulitis can be suspected by clinical findings alone, however radiological imaging is usually used to confirm the diagnosis and grade the severity.

Abdominal computed tomography (CT) is the primary tool for imaging. The findings suggestive of acute diverticulitis on CT include the presence of localized thickening of bowel wall (>4 mm), an increase in soft tissue density secondary to inflammation or fat stranding in pericolonic fat, and the presence of colonic diverticula (29, 30). Abdominal CT sensitivity and specificity are 94% and 99% respectively, for acute diverticulitis diagnosis (31). Diverticulitis complications could be directly visualized on an abdominal CT scan. For example, abscesses are identified as localized fluid collections contained within a cavity and surrounded by an area of inflammatory changes. The cavity center may contain air-fluid levels or necrotic debris (32). In addition to that, an

abdominal CT scan could visualize distended proximal bowel loops containing air–fluid levels in patients with bowel obstruction secondary to acute diverticulitis. In patients with peritonitis, free air could also be visualized on an abdominal CT scan. Thus abdominal CT imaging allows the clinician to accurately assess the severity of the diverticulitis episode and its complications, if any.

Acute diverticulitis classification:

To date, there have been many classifications for diverticulitis proposed in the literature, some of which are based on abdominal CT findings. Other classifications focus on clinical features of diverticular disease or are based on endoscopic assessment of colonic diverticular disease. One of the most widely recognized classification systems was initially proposed by Hinchey in 1978 (33). Modified versions of the Hinchey classification have been documented since then and are commonly used in medical practice (34). These modifications extended the initial clinical Hinchey classification to a modified classification that was based on CT findings. Furthermore, the modified classification encompasses the entire spectrum of diverticulitis rather than just perforated diverticulitis. Accordingly, uncomplicated diverticulitis with colonic wall inflammation only is called Stage 0 in the Modified Hinchey classification. A distinction was also created between confined pericolic phlegmon (Stage Ia) and a confined pericolic abscess (Stage Ib). The Hansen/Stock classification (35) accounted for asymptomatic diverticulosis in addition to complicated diverticulitis in various phases, depending on the severity of complications. In 1999, Köhler et al. also described a clinical classification that distinguished uncomplicated, complicated and recurrent disease (36). Ambrosetti et al. further classified patients into moderate diverticulitis and severe diverticulitis (37). The following tables compare the different well-known classifications.

Table 1: Comparison between different classifications systems based on abdominal CT

	Hinchey classification	**Köhler modification**	**Modified Hinchey**	**Hansen/Stock**
			0 Mild clinical diverticulitis	0 Diverticulosis
Stage I	Pericolic abscess confined by the mesocolon	Pericolic abscess	I Pericolic abscess or phlegmon Ia Colonic wall thickening/ confined pericolic inflammation Ib Confined small (<5 cm) pericolic abscess	I Acute uncomplicated diverticulitis
Stage II	Pelvic abscess, distant from area of inflammation	IIa Distant abscess amenable to percutaneous drainage IIb Complex abscess with/ without associated fistula	II Pelvic, distant intra-abdominal, or retroperitoneal abscess	Acute complicated diverticulitis IIa Phlegmon, peridiverticulitis IIb Abscess, sealed perforation IIc Free perforation
Stage III	Generalised peritonitis resulting from pericolic/pelvic abscess rupture into peritoneal cavity	Generalised purulent peritonitis	III Generalised purulent peritonitis	Recurrent diverticulitis
Stage IV	Faecal peritonitis resulting from free perforation of colonic diverticulum	Faecal peritonitis	IV Generalised faecal peritonitis	N/A

Table 2: Ambrosetti classification system.

Moderate diverticulitis	**Severe diverticulitis**
Localised sigmoid colon wall thickening (>5 mm) Inflammation localised to pericolic fat	Moderate diverticulitis plus any of: Abdominopelvic abscess Free extraluminal gas Extraluminal contrast extravasation

Management of Acute Diverticulitis:

The treatment of acute diverticulitis relies on the severity of presentation, presence of secondary complications, and the patient's comorbidities.

Uncomplicated diverticulitis

Bowel rest, IV hydration, and antibiotics are considered the standard treatment for acute diverticulitis. Treatment with antibiotics has relied on the long-standing assumption that diverticulitis was caused by colonic micro-perforation - a theory that is currently under heavy debate (36). As such, the role of antibiotics has become controversial, particularly with newly developed hypotheses centering on inflammation being solely responsible for the development of certain subsets of mild acute diverticulitis (38).

Complicated diverticulitis

Approximately 20% of patients presenting with diverticulitis develop a localized abscess near the inflamed colon, in the pelvis or in the nearby retroperitoneal space. Treatment with wide-spectrum antibiotics is effective in 70% of patients with an abscess less than 4 cm (39). If the abscess size is large or the treatment with antibiotics fails, then percutaneous drainage or surgery is the alternative line of treatment (39). Up to 80% of patients presenting with diverticular abscesses have successful percutaneous drainage (40).

On the other hand, about 6% of patients who present with severe complicated diverticulitis have a perforation with generalized peritonitis (40). Operative treatment for patients with Hinchey III, IV diverticulitis or in patients whose conditions were not improved by percutaneous abscess drainage is considered the best option (40). Nowadays, the standard operation in the emergency settings is

a resection with primary anastomosis with or without a diverting ileostomy, or a Hartmann's procedure.

Recurrent diverticulitis - incidence and risk factors

Complicated cases of diverticulitis, necessitating operative intervention, occur in only a small subset of patients with diverticulitis (41). Most initial episodes of diverticulitis are successfully managed non-operatively. However, approximately 20% to 50% of those patients are at risk of developing another episode of diverticulitis in the future (42-44). However, recurrent diverticulitis attacks are not associated with a higher risk of complications as compared with the first attack (42-44). In one series, only 5.5% of patients with recurrent diverticulitis underwent urgent surgery, and the rest of the patients underwent conservative non-operative management (41). In a population-based study, of 3222 patients with acute diverticulitis, recurrence occurred after the first and second episodes of diverticulitis at a rate of 22% and 55%, respectively over a 10-year period (42-44).

While most of these recurrent uncomplicated episodes can be managed non-operatively (52), thus eliminating any burdens caused by a surgery, they still pose a significant impact on patients' quality of life (55). Recovering from an acute uncomplicated episode is largely dependent on pain management and following a certain diet to normalize bowel habits (55). As such, recovery time can impose various limits on patients' daily activities, their social life, as well as create an economic burden if time off from work is necessary for recovery.

Furthermore, recurrent diverticulitis can contribute to an increase in health-related anxiety due to the unpredictability of recurrent episodes and their associated impacts on daily life (55).

Risk factors of recurrent diverticulitis

Literature on the risk factors associated with recurrence is currently incomplete and consists of retrospective cohort studies with small datasets. As such, there are no clear guidelines or predictors that can aid clinicians when counselling patients on recurrence. Some risk factors described in the literature, albeit limited, include:

- **Age***:* Several studies reported that younger age has a higher risk of recurrent diverticulitis. For example, a retrospective study of 1046 patients reported that patients age ≤ 40 years might have a higher risk of recurrence (multivariate HR 5.01, 95% CI 1.25–20.08) (43).
- **Gender***:* Female gender was found to be associated with recurrence in many studies. The increased risk for females is not dramatic and in one study it was estimated as a HR 1.14, 95% CI 1.02–1.29 (45).
- **Abscess formation at the primary episode***:* Several retrospective studies reported that recurrence risk is increased when the patient presented primarily with diverticular abscess. In addition to that, one study reported that the risk increased even more when the patient presented with more than one abscess (46, 47)
- **Inflammatory location and extension***:* Two studies evaluated the impact of the inflammatory location within the colon and its extension on recurrence risk, they found that an inflamed segment >5 cm and a left-sided location of the diverticulitis increased the risk of recurrence. (42, 48)
- **Number of previous recurrences***:* Several studies described an increased risk of recurrence with a history of prior recurrent diverticulitis attacks. A study by Rose J et al. reported a 9% recurrence rate at 1 year after the primary admission; a 36% recurrence rate

at 1 year after the second attack; and 65% risk of recurrence at 1 year after the third attack (49).

- **Immunocompromised patients***:* Some studies reported that immunocompromised patients usually present with severe diverticulitis and that they experience higher recurrence rates. This was observed in patients who are on chronic corticosteroids (50).
- **C-reactive protein (CRP) levels***:* Several studies found that an episode of primary diverticulitis with a high CRP level (>240 mg/l) was associated with significantly higher risk of recurrence (HR 1.75, 95% CI 1.04–2.94) (51)

An interesting, yet understudied risk factor is family history of diverticulitis. Only one retrospective study reported on family to be at increased risk of recurrence (HR 2.16; 95% CI 1.44–3.23). This observation suggests that genetic and environmental factors may be significantly increasing the recurrence of this disease (42).

Management of recurrent diverticulitis

In the past, the American Society of Colon and Rectal Surgeons (ASCRS) recommended that elective prophylactic colectomy should be offered to patients after two attacks of uncomplicated diverticulitis or after one attack of complicated acute diverticulitis.(52). However, several studies have shown that the majority of these recurrences are benign and can be treated conservatively, with only a small subset of patients being at risk of complicated recurrence and requiring surgery. In addition, elective surgery for diverticulitis comes with operative risks that must be weighed against its potential benefits. Furthermore, many argue that elective surgery after successful non-operative management does not reduce diverticulitis-related complications or mortality (53). As a result, the current ASCRS guidelines recommend that the decision for surgery should be

individualized to each patient considering their existent risk factors (54). Thus, identification of risk factors that increase a patient's risk of recurrent attacks, can be used to counsel patients and aid the decision-making process.

Gaps in knowledge and thesis objectives

Management strategies have changed in recent years because of increasing evidence that support non-operative approaches. However, uncertainty and inconsistency in regards to predictors of recurrent episodes has resulted in challenges in treatment decision making. However, most reports are from small single cohort studies; few population-based studies have been published to date. Moreover, existing studies have not taken into the account other predictors, such as family history of diverticulitis. Only one study reported on family history, suggesting a genetic or an environmental component influencing the disease. Understanding the role of family history as a risk factor for recurrent diverticulitis would be useful for surgeons when counselling patients regarding the risks of recurrence and the indications for elective colectomy. This thesis aimed to address the impact of family history on recurrent diverticulitis.

Objectives

The objectives of this thesis are three-fold:

1. To evaluate the association between the family history of diverticulitis and recurrence after an episode of successful non-operative management of diverticulitis.
2. To assess the impact of number of family members with a positive history of diverticulitis. as a predictor of disease recurrence.
3. To assess the impact of family history on the occurrence of a recurrent complicated episode of diverticulitis.

References

1. Painter NS, Burkitt DP. Diverticular disease of the colon, a 20th century problem. Clin Gastroenterol. 1975;4(1):3-21.
2. Peery AF, Barrett PR, Park D, Rogers AJ, Galanko JA, Martin CF, et al. A high-fiber diet does not protect against asymptomatic diverticulosis. Gastroenterology. 2012;142(2):266-72.e1.
3. Weizman AV, Nguyen GC. Diverticular disease: epidemiology and management. Can J Gastroenterol. 2011;25(7):385-9.
4. Strate LL, Modi R, Cohen E, Spiegel BM. Diverticular disease as a chronic illness: evolving epidemiologic and clinical insights. Am J Gastroenterol. 2012;107(10):1486-93.
5. Shahedi K, Fuller G, Bolus R, Cohen E, Vu M, Shah R, et al. Long-term risk of acute diverticulitis among patients with incidental diverticulosis found during colonoscopy. Clin Gastroenterol Hepatol. 2013;11(12):1609-13.
6. Etzioni DA, Mack TM, Beart RW, Jr., Kaiser AM. Diverticulitis in the United States: 1998-2005: changing patterns of disease and treatment. Ann Surg. 2009;249(2):210-7.
7. Teetor T, Palachick B, Grim R, Bell T, Martin J, Blumberg D, et al. The Changing Epidemiology of Diverticulitis in the United States. Am Surg. 2017;83(4):e134-e6.
8. Meyers MA, Alonso DR, Gray GF, Baer JW. Pathogenesis of bleeding colonic diverticulosis. Gastroenterology. 1976;71(4):577-83.
9. Golder M, Burleigh DE, Belai A, Ghali L, Ashby D, Lunniss PJ, et al. Smooth muscle cholinergic denervation hypersensitivity in diverticular disease. Lancet. 2003;361(9373):1945-51.
10. Bottner M, Barrenschee M, Hellwig I, Harde J, Egberts JH, Becker T, et al. The enteric serotonergic system is altered in patients with diverticular disease. Gut. 2013;62(12):1753-62.
11. Banerjee S, Akbar N, Moorhead J, Rennie JA, Leather AJ, Cooper D, et al. Increased presence of serotonin-producing cells in colons with diverticular disease may indicate involvement in the pathophysiology of the condition. Int J Colorectal Dis. 2007;22(6):643-9.
12. Afzal NA, Thomson M. Diverticular disease in adolescence. Best Pract Res Clin Gastroenterol. 2002;16(4):621-34.
13. Santin BJ, Prasad V, Caniano DA. Colonic diverticulitis in adolescents: an index case and associated syndromes. Pediatr Surg Int. 2009;25(10):901-5.

14. Granlund J, Svensson T, Olen O, Hjern F, Pedersen NL, Magnusson PK, et al. The genetic influence on diverticular disease--a twin study. Aliment Pharmacol Ther. 2012;35(9):1103-7.
15. Daniels L, Budding AE, de Korte N, Eck A, Bogaards JA, Stockmann HB, et al. Fecal microbiome analysis as a diagnostic test for diverticulitis. Eur J Clin Microbiol Infect Dis. 2014;33(11):1927-36.
16. Jacobs DO. Clinical practice. Diverticulitis. N Engl J Med. 2007;357(20):2057-66.
17. Painter NS. The cause of diverticular disease of the colon, its symptoms and its complications. Review and hypothesis. J R Coll Surg Edinb. 1985;30(2):118-22.
18. Markham NI, Li AK. Diverticulitis of the right colon--experience from Hong Kong. Gut. 1992;33(4):547-9.
19. Rodkey GV, Welch CE. Changing patterns in the surgical treatment of diverticular disease. Ann Surg. 1984;200(4):466-78.
20. Swanson SM, Strate LL. Acute Colonic Diverticulitis. Ann Intern Med. 2018;168(9):Itc65-itc80.
21. Parks TG. Natural history of diverticular disease of the colon. Clin Gastroenterol. 1975;4(1):53-69.
22. Parks TG. Natural history of diverticular disease of the colon. A review of 521 cases. Br Med J. 1969;4(5684):639-42.
23. Bahadursingh AM, Virgo KS, Kaminski DL, Longo WE. Spectrum of disease and outcome of complicated diverticular disease. Am J Surg. 2003;186(6):696-701.
24. Constantinides VA, Tekkis PP, Athanasiou T, Aziz O, Purkayastha S, Remzi FH, et al. Primary resection with anastomosis vs. Hartmann's procedure in nonelective surgery for acute colonic diverticulitis: a systematic review. Dis Colon Rectum. 2006;49(7):966-81.
25. Cirocchi R, Afshar S, Shaban F, Nascimbeni R, Vettoretto N, Di Saverio S, et al. Perforated sigmoid diverticulitis: Hartmann's procedure or resection with primary anastomosis-a systematic review and meta-analysis of randomised control trials. Tech Coloproctol. 2018.
26. Kriwanek S, Armbruster C, Beckerhinn P, Dittrich K. Prognostic factors for survival in colonic perforation. Int J Colorectal Dis. 1994;9(3):158-62.
27. Ambrosetti P, Robert JH, Witzig JA, Mirescu D, Mathey P, Borst F, et al. Acute left colonic diverticulitis: a prospective analysis of 226 consecutive cases. Surgery. 1994;115(5):546-50.

28. Kechagias A, Sofianidis A, Zografos G, Leandros E, Alexakis N, Dervenis C. index C-reactive protein predicts increased severity in acute sigmoid diverticulitis. Therapeutics and clinical risk management. 2018;14:1847.
29. Birnbaum BA, Balthazar EJ. CT of appendicitis and diverticulitis. Radiol Clin North Am. 1994;32(5):885-98.
30. Goh V, Halligan S, Taylor SA, Burling D, Bassett P, Bartram CI. Differentiation between diverticulitis and colorectal cancer: quantitative CT perfusion measurements versus morphologic criteria--initial experience. Radiology. 2007;242(2):456-62.
31. Lameris W, van Randen A, Bipat S, Bossuyt PM, Boermeester MA, Stoker J. Graded compression ultrasonography and computed tomography in acute colonic diverticulitis: meta-analysis of test accuracy. Eur Radiol. 2008;18(11):2498-511.
32. Snyder MJ. Imaging of colonic diverticular disease. Clin Colon Rectal Surg. 2004;17(3):155-62.
33. Hinchey EJ, Schaal PG, Richards GK. Treatment of perforated diverticular disease of the colon. Adv Surg. 1978;12:85-109.
34. Wasvary H, Turfah F, Kadro O, Beauregard W. Same hospitalization resection for acute diverticulitis. Am Surg. 1999;65(7):632-5; discussion 6.
35. Hansen O, Graupe F, Stock W. Prognostic factors in perforating diverticulitis of the large intestine. Der Chirurg; Zeitschrift fur alle Gebiete der operativen Medizen. 1998;69(4):443-9.
36. Köhler L, Sauerland S, Neugebauer E, Caprilli R, Fingerhut A, Haboubi N, et al. Diagnosis and treatment of diverticular disease. Surgical endoscopy. 1999;13(4):430-6.
37. Ambrosetti P, Becker C, Terrier F. Colonic diverticulitis: impact of imaging on surgical management–a prospective study of 542 patients. European radiology. 2002;12(5):1145-9.
38. Stollman N, Smalley W, Hirano I. American Gastroenterological Association Institute Guideline on the Management of Acute Diverticulitis. Gastroenterology. 2015;149(7):1944-9.
39. Ambrosetti P, Chautems R, Soravia C, Peiris-Waser N, Terrier F. Long-term outcome of mesocolic and pelvic diverticular abscesses of the left colon: a prospective study of 73 cases. Dis Colon Rectum. 2005;48(4):787-91.
40. Andeweg CS, Mulder IM, Felt-Bersma RJ, Verbon A, van der Wilt GJ, van Goor H, et al. Guidelines of diagnostics and treatment of acute left-sided colonic diverticulitis. Dig Surg. 2013;30(4-6):278-92.

41. Ritz JP, Lehmann KS, Frericks B, Stroux A, Buhr HJ, Holmer C. Outcome of patients with acute sigmoid diverticulitis: multivariate analysis of risk factors for free perforation. Surgery. 2011;149(5):606-13.

42. Hall JF, Roberts PL, Ricciardi R, Read T, Scheirey C, Wald C, et al. Long-term follow-up after an initial episode of diverticulitis: what are the predictors of recurrence? Dis Colon Rectum. 2011;54(3):283-8.

43. Binda GA, Arezzo A, Serventi A, Bonelli L, Facchini M, Prandi M, et al. Multicentre observational study of the natural history of left-sided acute diverticulitis. Br J Surg. 2012;99(2):276-85.

44. Makela JT, Kiviniemi HO, Laitinen ST. Spectrum of disease and outcome among patients with acute diverticulitis. Dig Surg. 2010;27(3):190-6.

45. Li D, de Mestral C, Baxter NN, McLeod RS, Moineddin R, Wilton AS, et al. Risk of readmission and emergency surgery following nonoperative management of colonic diverticulitis: a population-based analysis. Annals of surgery. 2014;260(3):423-31.

46. Devaraj B, Liu W, Tatum J, Cologne K, Kaiser AM. Medically treated diverticular abscess associated with high risk of recurrence and disease complications. Diseases of the Colon & Rectum. 2016;59(3):208-15.

47. Gregersen R, Andresen K, Burcharth J, Pommergaard H-C, Rosenberg J. Short-term mortality, readmission, and recurrence in treatment of acute diverticulitis with abscess formation: a nationwide register-based cohort study. International journal of colorectal disease. 2016;31(5):983-90.

48. Pittet O, Kotzampassakis N, Schmidt S, Denys A, Demartines N, Calmes J-M. Recurrent left colonic diverticulitis episodes: more severe than the initial diverticulitis? World journal of surgery. 2009;33(3):547.

49. Rose J, Parina RP, Faiz O, Chang DC, Talamini MA. Long-term Outcomes After Initial Presentation of Diverticulitis. Ann Surg. 2015;262(6):1046-53.

50. Biondo S, Borao JL, Kreisler E, Golda T, Millan M, Frago R, et al. Recurrence and virulence of colonic diverticulitis in immunocompromised patients. The American Journal of Surgery. 2012;204(2):172-9.

51. Buchs N, Konrad-Mugnier B, Jannot AS, Poletti PA, Ambrosetti P, Gervaz P. Assessment of recurrence and complications following uncomplicated diverticulitis. British Journal of Surgery. 2013;100(7):976-9.

52. Rafferty J, Shellito P, Hyman NH, Buie WD. Practice parameters for sigmoid diverticulitis. Diseases of the colon & rectum. 2006;49(7):939-44.

53. Eglinton T, Nguyen T, Raniga S, Dixon L, Dobbs B, Frizelle F. Patterns of recurrence in patients with acute diverticulitis. British Journal of Surgery. 2010;97(6):952-7.

54. Feingold D, Steele SR, Lee S, Kaiser A, Boushey R, Buie WD, et al. Practice parameters for the treatment of sigmoid diverticulitis. Diseases of the Colon & Rectum. 2014;57(3):284-94.

55. Spiegel BM, Reid MW, Bolus R, Whitman CB, Talley J, Dea S, Shahedi K, Karsan H, Teal C, Melmed GY, Cohen E. Development and validation of a disease-targeted quality of life instrument for chronic diverticular disease: the DV-QOL. Quality of Life Research. 2015 Jan 1;24(1):163-79.

Chapter 2: Family History as Predictor of recurrent diverticulitis After Episode of Uncomplicated Diverticulitis

Purpose: The purpose of this study was to evaluate the association between family history (FH) and recurrence after an episode of diverticulitis managed non-operatively.

Methods: After institutional review board approval, all patients with CT-proven left-sided diverticulitis who were managed non-operatively at our institutions from 2007-2017 were identified retrospectively. All CT scans of diverticulitis were reviewed by a blinded expert gastrointestinal radiologist. A detailed telephone follow-up questionnaire was conducted to assess for the presence of family history. The primary outcome was diverticulitis recurrence occurring >60 days following the index episode. A multiple Cox regression model was used to assess for an association between a positive FH and diverticulitis recurrence.

Results: Of the 997 patients identified with left-sided acute diverticulitis in the database, 476 completed the telephone questionnaire on FH of diverticulitis and were included in the analysis (response rate: 47.7%). Among them, 212 (44.5%) had a FH of diverticulitis and 264 (55.5%) did not. Compared to patients with no FH, patients with FH were similar in median age (61.0 vs. 62.5 years, p=0.14), proportion of male patients (45.3% vs. 43.2%, p=0.71). CT-characteristics of the index episode of acute diverticulitis were similar between the two groups; however, patients with FH had a higher incidence of abscess (27.8% vs. 4.5%, p<0.001).

Patients with a positive FH had a significantly higher incidence of diverticulitis recurrence than those with no FH (64.6% vs. 21.6%, p<0.001). On Cox regression, a positive FH remained

associated with diverticulitis recurrence (HR: 4.07, 95% CI 2.95-5.63, p<0.001). Also, it remained associated with the development of >1 recurrence (i.e., a re-recurrence) (HR: 2.07, 95% CI 1.17-3.64, p<0.001) and remained associated with the development of a complicated recurrence (HR: 9.75, 95% CI 4.11-23.10, p<0.001). Furthermore, patients with >1 relative with a history of diverticulitis had higher hazard of recurrence (HR: 2.12, 95% CI 1.50-3.00, p<0.001) compared to patients with only 1 relative.

Conclusions: Patients with a positive FH of diverticulitis are at higher risk for recurrent diverticulitis. A thorough FH of diverticulitis should be obtained when counselling patients regarding the risk of recurrence and the indications for elective colectomy.

Introduction

Colonic diverticular disease is common in western countries and is responsible for substantial socioeconomic burden [5]. Most people with diverticulosis remain asymptomatic; however, approximately 4% of patients will ultimately develop diverticulitis [21]. While the majority of patients with acute diverticulitis are successfully managed nonoperatively [54], recurrent episodes of diverticulitis are common, ranging between 20-40% [5, 40, 54, 55].

The pathophysiological mechanisms involved in the progression of diverticulosis to acute diverticulitis, as well as in the development of recurrent diverticulitis, remain poorly understood [56]. One patient-level factor that is often considered, but poorly studied, is the genetic predisposition for diverticulitis [56-59]. Diverticular disease has been previously associated with several inherited connective tissue diseases, such as Ehlers–Danlos syndrome [60, 61], Williams syndrome [62], Marfan syndrome [63] and polycystic kidney disease [64]. Additionally, in two large twin studies using nationwide patient registries, investigators provided evidence that genetic factors contribute significantly to the susceptibility of diverticular disease, estimating that heritability may be in the range of 40–53% [5, 14, 65]. Recently, the first genome-wide association study was performed and identified three loci associated with the risk of developing diverticulosis, which could be helpful in understanding the pathophysiology of diverticulitis [66]. However, the importance of these genetic factors on the development of recurrent diverticulitis has not yet been demonstrated.

At a clinical level, numerous observational studies have reported on risk factors of recurrent diverticulitis [40, 67-69], yet family history (FH) is often not studied. Hupfeld et al. recently published a comprehensive systematic review on predictors of recurrent diverticulitis

[70]; of the 35 included studies, only one was found to report on FH as a predictor of recurrent diverticulitis. Hall et al. reported a 2-fold increased odds of recurrence among patients with a positive FH (HR 2.16; 95% CI 1.44–3.23) [40]. However, their study did not describe how FH was elicited, nor whether or not FH was associated with other negative diverticulitis outcomes.

The purpose of this study was to evaluate for an association between FH of diverticulitis and recurrent diverticulitis after successful nonoperative treatment of an episode of acute diverticulitis. Our *a priori* hypothesis was that a positive FH of diverticulitis would be positively associated with diverticulitis recurrence.

Methods

Inclusion Criteria

This was an institutional review board–approved retrospective cohort study using a prospectively maintained database of all patients treated at the Jewish General Hospital and Montreal General Hospital with acute diverticulitis from January 2007 to April 2017. All cases of computed tomography (CT) scan–proven left sided acute diverticulitis were identified, and only those patients who were successfully managed nonoperatively were additionally reviewed and included for analysis. Nonoperative management was defined as the use of antibiotics, with or without percutaneous drainage, for the index episode of diverticulitis. We excluded patients who underwent emergency colectomy during their index admission or semi-urgent colectomy within 60 days of presentation, as well as patients with diverticulitis proximal to the splenic flexure.

Radiological Assessment

All CT scans pertaining to the index episode of diverticulitis were reviewed by two expert gastrointestinal radiologists who were blinded to our study objectives (V.P. and C.R.). In addition

to confirming the diagnosis of diverticulitis, they measured the length of colon involved (in centimeters) and the wall thickness (in millimeters) at the thickest point. Furthermore, the radiologists characterized the location of diverticulitis (sigmoid, descending, or both) and the severity of the episode. Severity was categorized similar to previous radiological classifications systems [21]: 1) uncomplicated: without visible perforation; 2) microperforation: air bubbles within 5cm of the affected area of colon and less than 0.5mm in size; 3) pericolonic macroperforation: air bubbles within 5cm of the affected area of colon and more than 0.5mm in size; 4) intraperitoneal perforation: air bubbles more than 5cm away from the affected area of colon (e.g. above the liver); 5) abscess: a fluid collection with a well-formed rim-enhancing wall; and 6) phlegmon: ill-defined confluent area of increased density on the adjacent fat that did not meet the definition of an abscess (i.e., no complete enhancing wall).

Data Collection and Follow-Up

Data regarding patient demographics and clinical variables were collected based on a review of the hospital electronic and paper medical charts. A Charlson Comorbidity Score (CCS) was calculated for each patient based on their reported comorbidities. Immunosuppression was defined as any of the following: chemotherapy within 6 weeks, HIV with CD4+ cell count <200/μL, steroid intake >5 mg of prednisone equivalent daily, or the presence of any other immunosuppressive medication, including methotrexate, biologics, and transplant immunosuppressants. Previous history of diverticulitis prior to the index episode was also collected.

Data regarding FH of diverticulitis was obtained via telephone questionnaire, which was conducted between July 2018 and December 2018. Patients were asked about any history of diverticulitis in the following blood relatives: parents, siblings, children, grandparents, aunts and

uncles, and cousins. A positive FH was defined as the presence of diverticulitis in any of the family members listed above (i.e. first or second degree FH). FH in a first-degree relative was limited to parents, siblings, and children, while FH in a second-degree relative was limited to grandparents, aunts and uncles, and cousins. Furthermore, the number of relatives with a positive FH was documented. Patients were also asked regarding any hospital admission and surgery for diverticulitis in those family members, in an attempt to truly capture cases of "diverticulitis" and not "diverticulosis". Only patients who were reached by telephone and who responded to the questionnaire were included in this study.

At the time of telephone follow-up, we also asked questions regarding the patient's personal diverticulitis history in order to capture all possible recurrent episodes. We documented whether or not they sought medical or surgical treatment for recurrent diverticulitis at another hospital since their index presentation, and updated data regarding diverticulitis recurrence. The date of last follow-up was the date of the telephone call, or patients were censored if they developed an event (i.e. recurrence) or underwent sigmoid colectomy during the follow-up period.

Outcomes

The primary outcome was diverticulitis recurrence, diagnosed either by CT scan or on clinical grounds by a Colorectal Surgeon in the emergency room, occurring >60 days following the index episode. This 60-day interval was used to distinguish persistent from recurrent diverticulitis, as has been used in previous studies [22, 23]. Secondary outcomes included the development of a complicated recurrence (defined as recurrent diverticulitis with an abscess, fistula, large bowel obstruction, or macroperforation requiring urgent surgery) and the development of >1 recurrence (i.e., a re-recurrence).

Statistical Analysis and Sample Size Calculations

Data are presented as medians with ranges (Q1-Q3) or percentages with 95% confidence intervals (CIs), as appropriate. Fisher exact, Student *t*, and Wilcoxon rank-sum tests were used for univariate analysis of categorical, normally distributed continuous, and non-normally distributed continuous variables, respectively. Kaplan-Meier survival curves and log-rank tests were used to compare recurrence-free survival in patients with FH and patients without FH. A multiple Cox proportional hazards model was used to assess for an association between FH of diverticulitis and recurrent diverticulitis, adjusting for age, sex, Charlson Comorbidity Score >2, personal history of diverticulitis, immunosuppression, extraluminal air, abscess, and inflammatory segment >5cm (factors previously established with diverticulitis recurrence in the literature) [20]. Sample size considerations were performed, assuming a baseline incidence of diverticulitis recurrence of 20% and an effect size of at least 2.2 [5] with 80% power and an alpha=0.05. Given a prevalence of positive FH in the cohort of anywhere between 30-50%, sample size calculations estimated that a maximum of 313 patients would be required.

Similar analyses were performed for each secondary outcome (complicated recurrence and re-recurrence), and censoring was adjusted to reflect the respective outcome. An alpha of 0.05 was used for statistical significance. All statistical analyses were performed with R v3.5.1 (R Development Core Team. 2017. *R: A Language and Environment for Statistical Computing*. Vienna, Austria).

Results

Of the 997 patients identified with left-sided acute diverticulitis in the database, 476 completed the telephone questionnaire on FH of diverticulitis and were included in the analysis (response rate: 47.7%). Among them, 212 (44.5%) had a FH of diverticulitis (129 patients with 1 relative only and 83 patients with >1 relative) and 264 (55.5%) did not. Of those with a positive FH (n=212), 190 patients had a first-degree FH, 37 had a second-degree FH, and 15 had both. Patients excluded from the analysis for not responding to the FH questionnaire had a higher incidence of immunosuppression but were otherwise similar to included patients **(Supplementary Table 1)**.

Compared to patients with no FH, patients with FH were similar in median age (61.0 vs. 62.5 years, p=0.14), proportion of male patients (45.3% vs. 43.2%, p=0.71), proportion of patients with a CCS >2 (46.7% vs. 44.7%, p=0.73), and past history of diverticulitis (9.4% vs. 6.4%, p=0.30). Patients with FH, however, had a higher incidence of immunosuppression (18.0% vs. 1.5%, p=<0.001). Radiological characteristics of the index episode of acute diverticulitis were similar between the two groups in terms of location in the colon, inflammatory thickness, and degrees of extraluminal air; however, patients with FH had a slightly longer median length of inflammation (6.1 vs. 5.7 cm, p=0.022) and had a higher incidence of abscess (27.8% vs. 4.5%, p<0.001). All patient, radiologic, and treatment characteristics are reported in **Table 1**.

After a median follow-up of 37.3 (14.7-63.2) months, the overall incidence of diverticulitis recurrence in the cohort was 40.8% (194/476) and 44 (9.2%) patients underwent sigmoid colectomy (30 elective and 14 urgent). Patients with a positive FH had a significantly higher

incidence of diverticulitis recurrence than those with no FH (64.6% vs. 21.6%, $p<0.001$) and had worse recurrence-free survival (log-rank test: $p<0.001$) **(Figure 1)**. On Cox proportional hazards regression, a positive FH remained associated with diverticulitis recurrence (HR: 3.84, 95% CI 2.77-5.33, $p<0.001$). Immunosuppression was the only other factor that was associated with diverticulitis recurrence on multivariate analysis (HR: 2.48, 95% CI 1.65-3.73, $p<0.001$) **(Table 2)**. When analyzed by degree of FH, first-degree FH alone was associated with diverticulitis recurrence (HR: 3.43, 95% CI 2.51-4.69, $p<0.001$) but second-degree FH alone was not (HR: 1.38, 95% CI 0.87-2.19, $p=0.17$). Furthermore, among only patients with a positive FH (n=212), patients with >1 relative with a history of diverticulitis had worse recurrence-free survival (log-rank test: $p<0.001$) **(Figure 2)** and higher hazards of recurrence on Cox regression (HR: 2.09, 95% CI 1.47-2.96, $p<0.001$) compared to patients with only 1 relative.

Sixty patients developed a complicated recurrence, representing 12.6% of the total cohort and 30.9% of patients who developed diverticulitis recurrence. The incidence of complicated recurrence was higher among patients with FH (25.0% vs. 2.7%, $p<0.001$), and patients with FH had worse complicated-recurrence-free survival compared to patients with no FH (log-rank test: $p<0.001$) **(Figure 3)**. On Cox regression, FH remained associated with the development of a complicated recurrence (HR: 7.91, 95% CI 3.50-17.85, $p<0.001$). In addition, immunosuppression (HR: 2.41, 95% CI 1.31-4.44, $p=0.005$) and the presence of an abscess on the index episode (HR: 1.82, 95% CI 1.01-3.31, $p=0.048$) were associated with complicated recurrence **(Table 3)**.

Among patients who developed a recurrence (n=194), 112 (57.7%) developed one recurrence only and 82 (42.2%) developed >1 recurrence (51 with two recurrences, 20 with three recurrences, 9 with four recurrences, and 2 with five recurrences). Patients with FH had worse recurrence-free survival after a first recurrence compared to patients with no FH (log-rank test:

p<0.021) **(Figure 4)**. On Cox regression, FH remained associated with the development of >1 recurrence (i.e., a re-recurrence) (HR: 2.14, 95% CI 1.21-3.78, p<0.001).

Discussion and limitations

Sigmoid diverticulitis is one of the most common and burdensome surgical conditions. While improvements in medical care and interventional radiology have resulted in higher success rates of nonoperative management, roughly 20-40% of patients will experience at least one recurrent episode [1, 3-5]. Given the important implications of recurrent diverticulitis on quality of life and treatment decisions [24], it is imperative that surgeons be able to predict patients at highest risk.

To our knowledge, this is the first study to focus on the relationship between FH of diverticulitis and recurrent diverticulitis. We demonstrated that patients with a positive FH experienced a near 4-fold increased hazards of diverticulitis recurrence compared to patients without FH of diverticulitis. This association was further strengthened by evaluating both the degree and number of relatives with a history of diverticulitis. We observed a higher hazards of recurrence among patients with a first-degree positive FH compared to second-degree, and among patients with more than one relative with a history of diverticulitis compared to one relative only. To date, only one previous study has reported FH as a predictor of recurrent diverticulitis. Hall et al. studied a multitude of patient and radiologic characteristics in a retrospective cohort study including 672 patients with a first episode of diverticulitis, and reported an adjusted hazards ratio for recurrent diverticulitis of 2.2 (95% CI 1.4-3.2) with a positive FH [5]. However, the authors did not elaborate on their means of collecting FH data, nor did they report on the impact of degree of FH and number of relatives. In colorectal cancer research, previous studies have highlighted the difficulties in obtaining reliable FH data; particularly when relying on patient charts, as the

information is often inaccurate or missing [25, 26]. In the present study, we performed a prospective telephone follow-up to collect data on FH rather than relying on previous medical notes.

There are a number of potential mechanisms that could explain the association between FH of diverticulitis and recurrent diverticulitis. Using the traditional twin study design, Granlund et al. studied 2,296 monozygotic and dizygotic twins from Sweden. They reported a 7-fold increased odds of developing diverticular disease in individuals with an affected monozygotic twin, and estimated that roughly 40% of the risk is contributed by genetic factors [15]. A recent genome-wide study also identified the first loci associated with diverticular disease, further honing in on the genetic predisposition for diverticulitis [17]. Furthermore, much of the increased risk of diverticulitis amongst family members could be due to shared environments. Several dietary (fiber deficiency, red meat, dietary fat) and lifestyle (physical inactivity, smoking) factors have been associated with diverticular disease [27-30]. While there is no strong evidence supporting these environmental factors as predictors of recurrent diverticulitis, they may be contributory. Appendicitis, which shares a similar pathophysiology to diverticulitis, also appears to aggregate in families. Several studies have reported a higher risk of appendicitis amongst patients with a positive FH of appendicitis, both in the pediatric and adult populations [31,32].

While the fear of diverticulitis being a progressive disease has mostly been rebuked [34], there are still a minority of patients who will develop a complicated recurrence after an uncomplicated index presentation. Our study demonstrated that patients with a positive FH were at significantly increased risk of developing a complicated recurrence, independent of the severity of their index episode. This could be another consideration when contemplating the decision to offer an elective colectomy. Immunosuppression and an abscess on the index episode were the

only other factors independently associated with a complicated recurrence, consistent with the literature [20, 35, 36].

The strengths of this study are the long follow-up time, the prospective telephone questionnaire to obtain detailed FH data, and the blinded expert radiological review of each patient's index episode CT scan. Our FH questionnaire assessed for diverticulitis history in multiple blood relatives, and specifically asked about hospitalizations and surgery to minimize misclassification of "diverticulosis" as "diverticulitis". However, there are a number of limitations that must be considered when interpreting our results. Roughly half of eligible patients did not complete the FH questionnaire and were excluded from the analysis, which could result in nonresponse bias. However, we were able to demonstrate that the demographic and index episode characteristics were similar between included and excluded patients, and a response rate of 47% is often considered good in this type of research [37, 38]. Questionnaire-based studies are also at risk of recall bias, as patients who experienced recurrent diverticulitis may be more likely to have remembered a FH of diverticulitis. Finally, this was a single-center study of Canadian patients, the results of which should be replicated before drawing definitive conclusions.

Conclusions and future implications

After an episode of acute diverticulitis managed nonoperatively, patients with a positive FH of diverticulitis are at higher risk for recurrent diverticulitis, as well as for the development of multiple recurrences and a complicated recurrence. A thorough FH of diverticulitis should be obtained when counselling patients regarding the risks of diverticulitis recurrence and the indications for elective colectomy. More research on the genetic predisposition of diverticulitis is needed to better understand the etiological role of FH in developing recurrent disease.

Table 1 – Patient, radiologic, and treatment characteristics of patients with and without family history of diverticulitis

	Positive FH n=212	**Negative FH n=264**	***P***
Patient			
Age, years, median, (Q1-Q3)	61.0 (50.0-71.0)	62.5 (53.0-72.0)	0.14
Male gender, n (%)	96 (45.3)	114 (43.2)	0.71
CCS >2, n (%)	99 (46.7)	118 (44.7)	0.73
Immunosuppression, n (%)	39 (18.4)	4 (1.5)	<0.001
Past diverticulitis, n (%)	20 (9.4)	17 (6.4)	0.30
Radiologic			
Location, n (%)	-	-	0.19
Sigmoid	141 (66.5)	163 (61.7)	-
Descending	48 (22.6)	57 (21.6)	-
Both	23 (10.8)	44 (16.7)	-
Length, mm, median (Q1-Q3)	61.0 (46.0-86.0)	57.0 (44.0-73.0)	0.022
Length >5cm, n (%)	145 (68.5)	164 (62.1)	0.18
Thickness, mm, median (Q1-Q3)	10.0 (8.0-12.0)	9.0 (7.0-11.0)	0.057
Microperforation, n (%)	15 (7.1)	31 (11.7)	0.12
Pericolonic macroperofration or intraperitoneal perforation, n (%)	21 (9.9)	19 (7.2)	0.37
Phlegmon, n (%)	7 (3.3)	12 (4.5)	0.65
Abscess, n (%)	59 (27.8)	12 (4.5)	<0.001
Treatment			
Admission, n (%)	118 (55.7)	127 (48.1)	0.12
Percutaneous drain, n (%)	27 (12.7)	7 (2.7)	0.004

FH = family history; CCS = Charlson Comorbidity Score

Table 2 – Cox proportional hazards model: Dependent variable = Recurrent diverticulitis

Covariate	**HR**	**95% CI**	***p***
Family history	3.84	2.77-5.33	<0.001
Age	0.99	0.98-1.1	0.78
Male sex	1.06	0.79-1.44	0.67
Immunosuppression	2.48	1.65-3.73	<0.001
Past diverticulitis	1.37	0.84-2.24	0.21
Inflammatory length >5cm	1.09	0.80-1.50	0.56
Extraluminal air	0.58	0.32-1.03	0.067
Abscess	0.88	0.60-1.29	0.51

HR = hazards ratio; CI = confidence interval

Table 3 – Cox proportional hazards model: Dependent variable = Complicated recurrent diverticulitis

Covariate	**HR**	**95% CI**	***p***
Family history	7.91	3.50-17.85	<0.001
Age	0.99	0.97-1.01	0.46
Male sex	0.96	0.56-1.63	0.87
Immunosuppression	2.41	1.31-4.44	0.005
Past diverticulitis	1.04	0.41-2.62	0.94
Inflammatory length >5cm	0.99	0.55-1.77	0.97
Extraluminal air	1.26	0.54-2.93	0.59
Abscess	1.82	1.01-3.31	0.048

HR = hazards ratio; CI = confidence interval

Supplementary Table 1 – Patient, radiologic, and treatment characteristics of patients included in the analysis and those who could not be contacted by telephone

	Included n=476	**Excluded n=521**	***p***
Patient			
Age, years, median, (Q1-Q3)	62.0 (52.0-72.0)	61.0 (53.0-70.0)	0.22
Male gender, n (%)	210 (44.1)	247 (47.4)	0.37
CCS >2, n (%)	217 (45.6)	231 (44.3)	0.62
Immunosuppression, n (%)	43 (9.0)	75 (14.4)	0.029
Past diverticulitis, n (%)	37 (7.8)	45 (8.6)	0.84
Radiologic			
Location, n (%)	-	-	0.45
Sigmoid	304 (63.9)	324 (62.1)	-
Descending	105 (22.1)	119 (22.8)	-
Both	67 (14.1)	77 (14.8)	-
Length, mm, median (Q1-Q3)	58.0 (45.0-80.0)	58.0 (44.0-86.0)	0.45
Length >5cm, n (%)	309 (64.9)	334 (64.1)	0.39
Thickness, mm, median (Q1-Q3)	9.0 (7.0-11.0)	9.0 (7.0-12.0)	0.79
Microperforation, n (%)	46 (9.7)	63 (12.1)	0.44
Pericolonic macroperofration or intraperitoneal perforation, n (%)	40 (8.4)	41 (7.9)	0.51
Phlegmon, n (%)	19 (4.0)	14 (2.7)	0.11
Abscess, n (%)	71 (14.9)	63 (12.1)	0.17
Treatment			
Admission, n (%)	245 (51.5)	236 (45.3)	0.10
Percutaneous drain, n (%)	34 (7.1)	25 (4.8)	0.13

FH = family history; CCS = Charlson Comorbidity Score

Figure 1 – Diverticulitis recurrence-free survival among patients with a positive and negative family history of diverticulitis

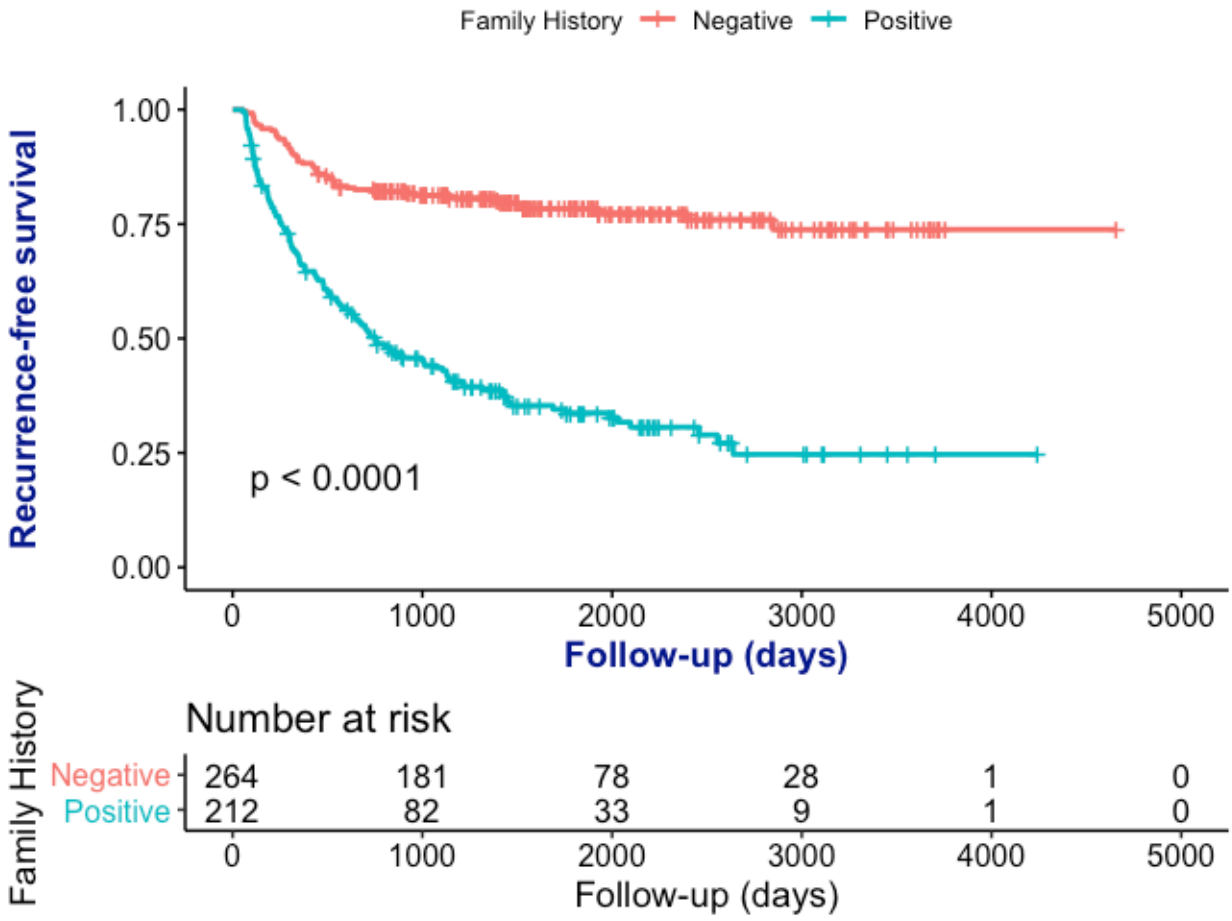


Figure 2 – Among patients with a positive family history for diverticulitis (n=212), diverticulitis recurrence-free survival for patients with >1 relative with a positive family history and patients with only one relative

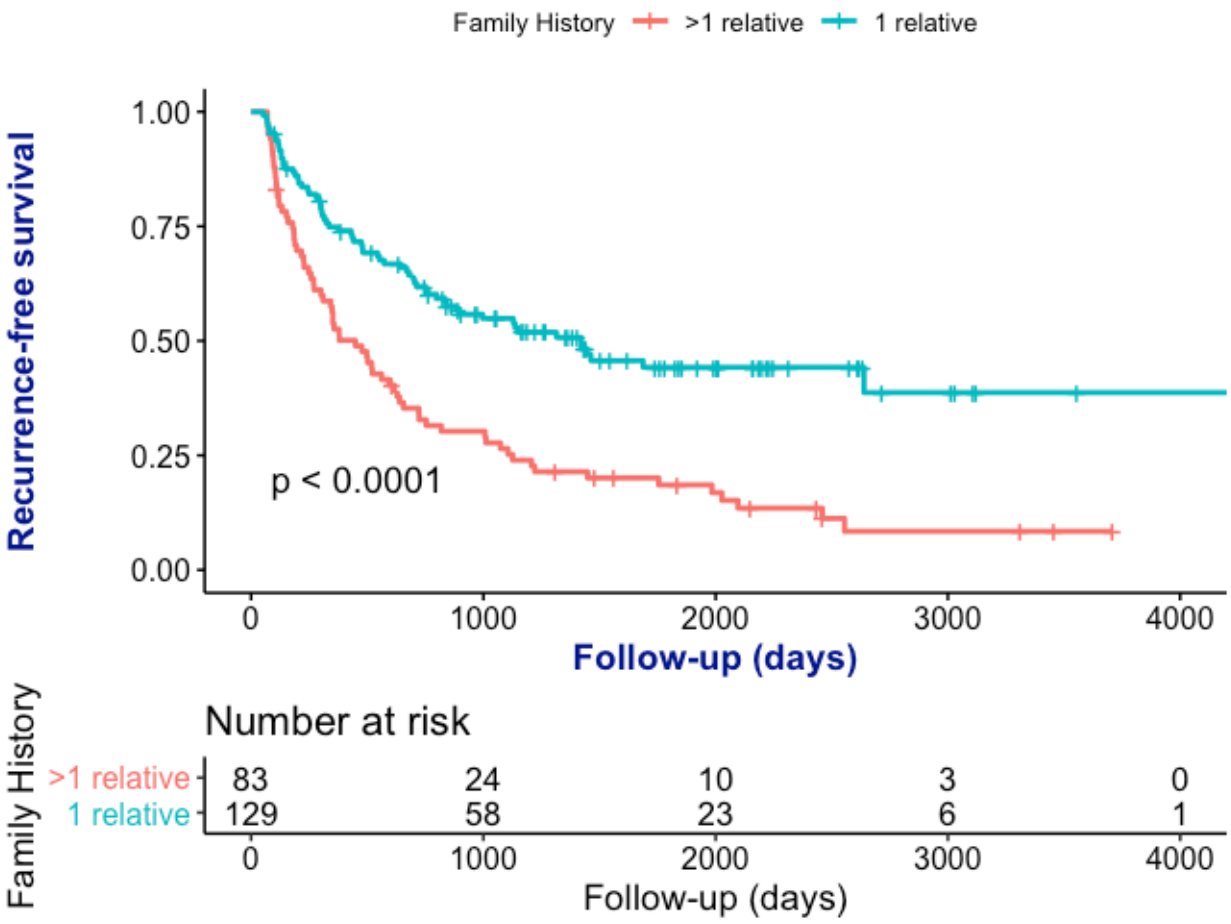


Figure 3 – Complicated diverticulitis recurrence-free survival among patients with a positive and negative family history of diverticulitis

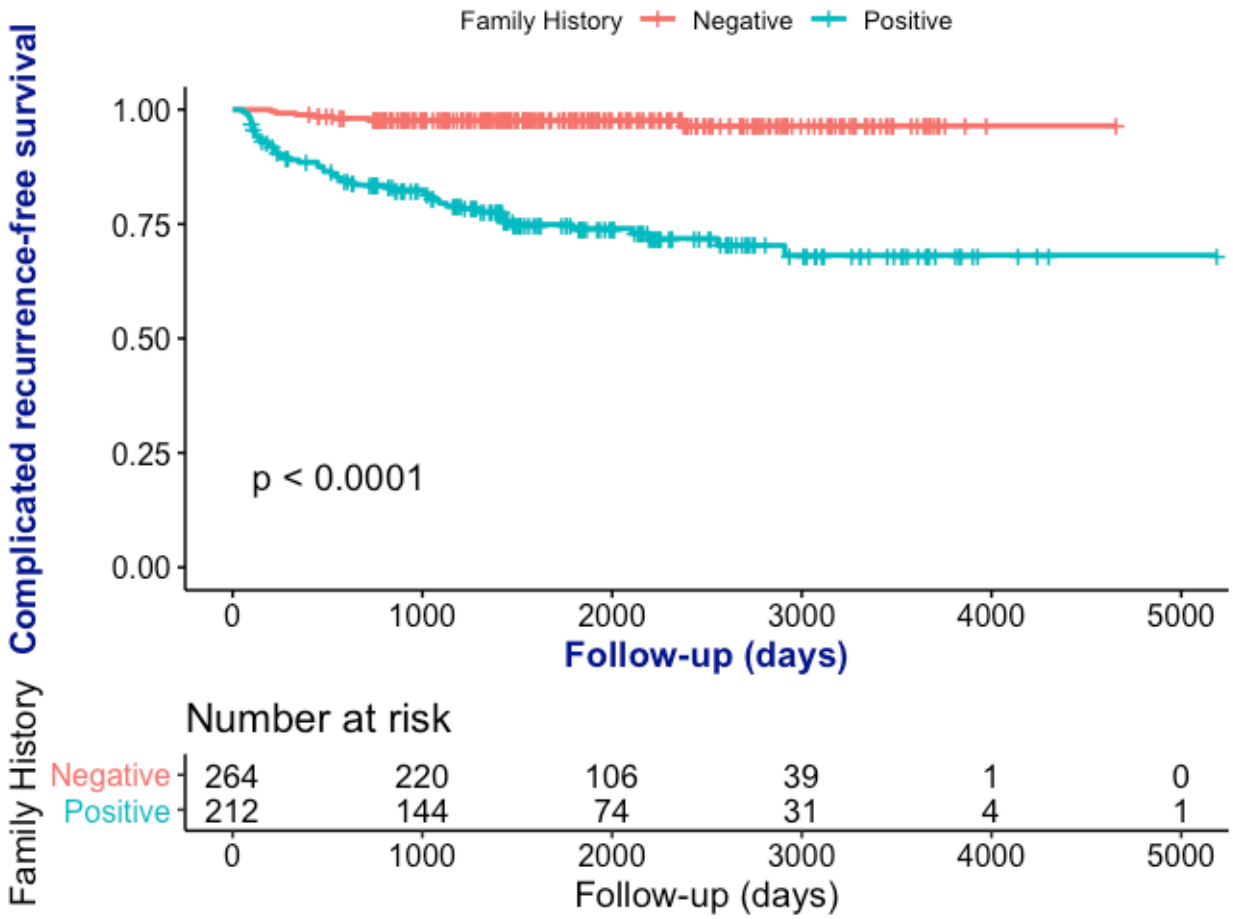
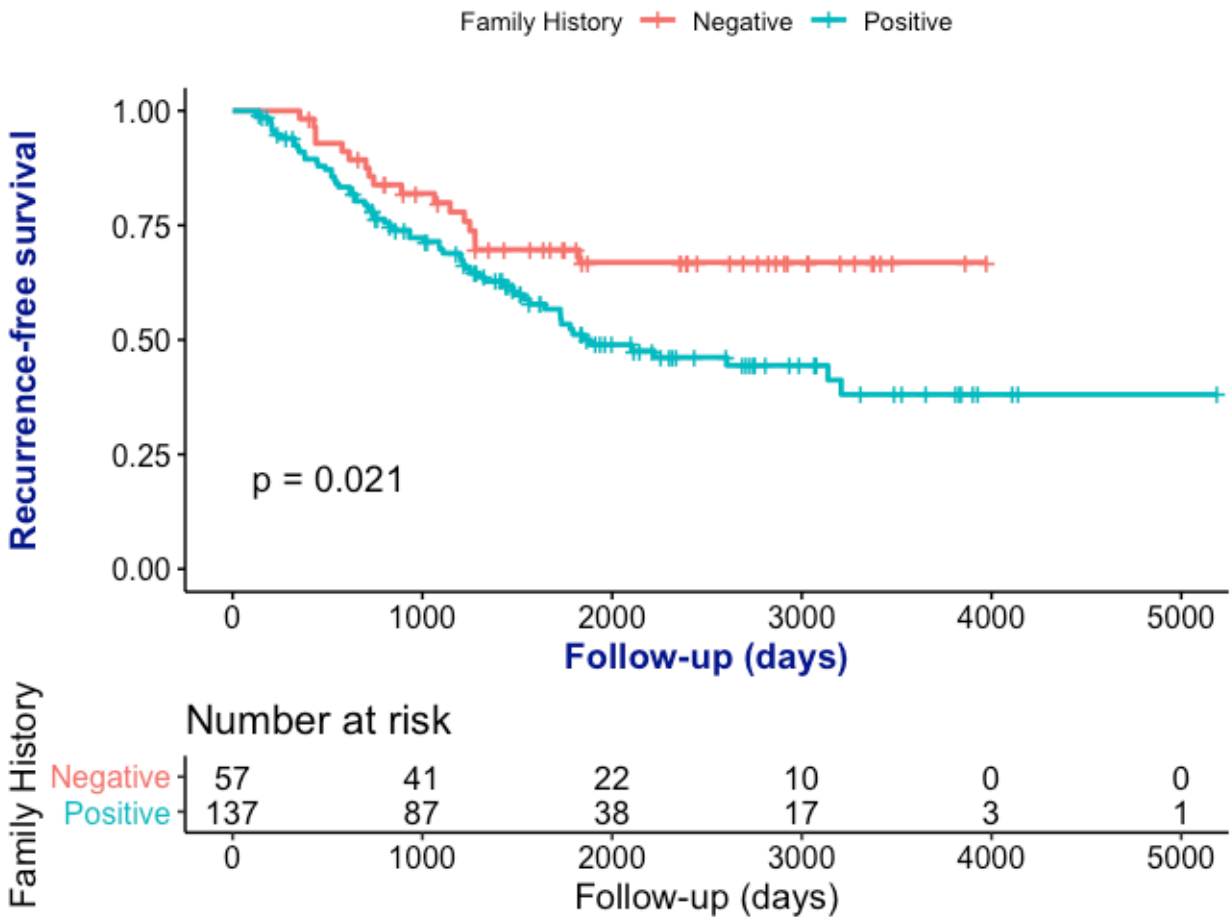


Figure 4 – Among patients with a first recurrence (n=194), diverticulitis recurrence-free survival ("re-recurrence") among patients with a positive and negative family history of diverticulitis



References

1. Shahedi K, Fuller G, Bolus R, Cohen E, Vu M, Shah R, et al. Long-term risk of acute diverticulitis among patients with incidental diverticulosis found during colonoscopy. Clin Gastroenterol Hepatol. 2013;11:1609-13.
2. Parks TG. Natural history of diverticular disease of the colon. Clin Gastroenterol. 1975;4:53-69.
3. Bharucha AE, Parthasarathy G, Ditah I, Fletcher JG, Ewelukwa O, Pendlimari R, et al. Temporal trends in the incidence and natural history of diverticulitis: a population-based study. Am J Gastroenterol. 2015;110:1589-96.
4. El-Sayed C, Radley S, Mytton J, Evison F, Ward ST. Risk of recurrent disease and surgery following an admission for acute diverticulitis. Dis Colon Rectum. 2018;61:382-9.
5. Hall JF, Roberts PL, Ricciardi R, Read T, Scheirey C, Wald C, Marcello PW, Schoetz DJ. Long-term follow-up after an initial episode of diverticulitis: what are the predictors of recurrence? Dis Colon Rectum. 2011;54:283-8.
6. Zullo A. Medical hypothesis: speculating on the pathogenesis of acute diverticulitis. Ann Gastroenterol. 2018;31:747.
7. Reichert MC, Lammert F. The genetic epidemiology of diverticulosis and diverticular disease: emerging evidence. United European Gastroenterol J. 2015;3:409-18.
8. Manousos O, Day NE, Tzonou A, Papadimitriou C, Kapetanakis A, Polychronopoulou-Trichopoulou A, Trichopoulos D. Diet and other factors in the aetiology of diverticulosis: an epidemiological study in Greece. Gut. 1985;26:544-9.
9. Connelly TM, Berg AS, Hegarty JP, Deiling S, Brinton D, Poritz LS, Koltun WA. The TNFSF15 gene single nucleotide polymorphism rs7848647 is associated with surgical diverticulitis. Ann Surg. 2014;259:1132-7.
10. Lindor NM, Bristow J. Tenascin-X deficiency in autosomal recessive Ehlers-Danlos syndrome. Am J Med Genet A. 2005;135:75-80.
11. Beighton PH, Murdoch JL, Votteler T. Gastrointestinal complications of the Ehlers-Danlos syndrome. Gut. 1969;10:1004-8.

12. Partsch CJ, Siebert R, Caliebe A, Gosch A, Wessel A, Pankau R. Sigmoid diverticulitis in patients with Williams-Beuren syndrome: relatively high prevalence and high complication rate in young adults with the syndrome. Am J Med Genet A. 2005;137:52-4.
13. Eliashar R, Sichel JY, Biron A, Dano I. Multiple gastrointestinal complications in Marfan syndrome. Postgrad Med J. 1998;74:495-7.
14. Pourfarziani V, Mousavi-Nayeeni SM, Ghaheri H, Assari S, Saadat SH, Panahi F, Noorbala MH, Vasei A, Norouzi AR, Simforoosh N. The outcome of diverticulosis in kidney recipients with polycystic kidney disease. Transplant Proc. 2007;39:1054-6.
15. Granlund J, Svensson T, Olen O, Hjern F, Pedersen NL, Magnusson PK, Schmidt PT. The genetic influence on diverticular disease--a twin study. Aliment Pharmacol Ther. 2012;35:1103-7.
16. Strate LL, Erichsen R, Baron JA, Mortensen J, Pedersen JK, Riis AH, Christensen K, Sorensen HT. Heritability and familial aggregation of diverticular disease: a population-based study of twins and siblings. Gastroenterology. 2013;144:736-42.
17. Sigurdsson S, Alexandersson KF, Sulem P, Feenstra B, Gudmundsdottir S, Halldorsson GH, et al. Sequence variants in ARHGAP15, COLQ and FAM155A associate with diverticular disease and diverticulitis. Nat Commun. 2017;8:15789. doi: 10.1038/ncomms15789.
18. Li D, de Mestral C, Baxter NN, McLeod RS, Moineddin R, Wilton AS, Nathens AB. Risk of readmission and emergency surgery following nonoperative management of colonic diverticulitis: a population-based analysis. Ann Surg. 2014;260:423-30.
19. Sallinen V, Mali J, Leppaniemi A, Mentula P. Assessment of risk for recurrent diverticulitis: a proposal of risk score for complicated recurrence. Medicine (Baltimore). 2015;94:e557.
20. Hupfeld L, Burcharth J, Pommergaard HC, Rosenberg J. Risk factors for recurrence after acute colonic diverticulitis: a systematic review. Int J Colorectal Dis. 2017;32:611-22.
21. Sartelli M, Moore FA, Ansaloni L, Di Saverio S, Coccolini F, Griffiths EA, et al. A proposal for a CT driven classification of left colon acute diverticulitis. World J Emerg Surg. 2015;10:3. doi:10.1186/1749-7922-10-3.

22. Garfinkle R, Kugler A, Pelsser V, Vasilevsky CA, Morin N, Gordon P, Feldman LS, Boutros M. Diverticular abscess managed with long-term nonoperative intent is safe. Dis Colon Rectum. 2016;59:648-55.
23. Etzioni DA, Chiu VY, Cannom RR, Burchette RJ, Haigh PI, Abbas MA. Outpatient treatment of acute diverticulitis: rates and predictors of failure. Dis Colon Rectum. 2010;53:861-5.
24. Andeweg CS, Berg R, Staal JB, ten Broek RPG, van Goor H. Patient-reported outcomes after conservative or surgical management of recurrent and chronic complaints of diverticulitis: systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2016;14:183-90.
25. Church J, McGannon E. Family history of colorectal cancer: how often and how accurately is it recorded? Dis Colon Rectum. 2000;43:1540-5.
26. Mitchell RJ, Brewster D, Campbell H, Porteous ME, Wyllie AH, Bird CC, Dunlop MG. Accuracy of reporting of family history of colorectal cancer. Gut. 2004;53:291-5.
27. Painter NS, Burkitt DP. Diverticular disease of the colon: a deficiency disease of Western civilization. Br Med J. 1971;2:450-4.
28. Hjern F, Wolk A, Hakansson N. Smoking and the risk of diverticular disease in women. Br J Surg. 2011;98:997-1002.
29. Strate LL, Liu YL, Aldoori WH, Giovannucci EL. Physical activity decreases diverticular complications. Am J Gastroenterol. 2009;104:1221-30.
30. Aldoori WH, Giovannucci EL, Rimm EB, Wing AL, Trichopoulos DV, Willett WC. A prospective study of diet and the risk of symptomatic diverticular disease in men. Am J Clin Nutr. 1994;60:757-64.
31. Gauderer MW, Crane MM, Green JA, DeCou JM, Abrams RS. Acute appendicitis in children: the importance of family history. J Pediatr Surg. 2001;36:1214-7.
32. Drescher MJ, Marcotte S, Grant R, Staff L. Family history is a predictor for appendicitis in adults in the emergency department. West J Emerg Med. 2012;13:468-71.
33. Wong WD, Wexner SD, Lowry A, Vernava A 3rd, Burnstein M, Denstman F, Fazio V, Kerner B, Moore R, Oliver G, Peters W, Ross T, Senatore P, Simmang C. The Standards Task Force, American Society of Colon and Rectal Surgeons. Practice parameters for the

treatment of sigmoid diverticulitis - supporting documentation. Dis Colon Rectum. 2000;43:290-7.

34. Chapman RJ, Dozois EJ, Wolff BG, Gullerud RE, Larson D. Diverticulitis: a progressive disease? Do multiple recurrences predict less favorable outcomes? Ann Surg. 2005;242:270-77.

35. Oor JE, Atema JJ, Boermeester MA, Vrouenraets BC, Unlu C. A systematic review of complicated diverticulitis in post-transplant patients. J Gastrointest Surg. 2014;18:2038-46.

36. Chapman J, Davies M, Wolff B, Dozois E, Tessier D, Harrington J, Larson D. Complicated diverticulitis: is it time to rethink the rules? Ann Surg. 2005;242:576-81.

37. Saunders CL, Elliott MN, Lyratzopoulos G, Abel GA. Do differential response rates to patient surveys between organizations lead to unfair performance comparisons? Evidence from the English Cancer Patient Experience Survey. Med Care. 2016;54:45-54.

38. Elliott MN, Cohea CW, Lehrman WG, Goldstein EG, Cleary PD, Giordano LA, Beckett MK, Zaslavsky AM. Accelerating improvement and narrowing gaps: trends in patients' experiences with hospital care reflected in HCAHPS public reporting. Health Serv Res. 2015;50:1850-67.

Chapter 3: Comprehensive discussion on our findings and future directions

The best treatment strategy for recurrent diverticulitis, be it medical management or elective prophylactic colectomy, continues to be heavily debated. This thesis demonstrated that family history is a significant predictor of recurrence of acute diverticulitis. There is only one other report in the literature which mentions family history as a predictor of recurrence. Hall et al.,in 2011, reported family history (reported as absent or present) as one of many predictors of recurrence but the data set analyzed in their publication was based on retrospective chart review alone, thus they could not explore degree of relatives, number of relatives or the impact on complicated recurrence. We interviewed patients by phone and obtained all the relevant details regarding family history. We found that patients with family history are more likely to develop more than one diverticulitis episode. Furthermore, patients with family history might have higher incidence of developing diverticular abscess than those without family history. Also, patients with >1 relative with family history had a higher risk of recurrence compared to patients with only 1 relative.

The importance of our findings should be viewed in the context of current diverticulitis treatment decision making. Historically, elective colectomy was recommended to patients after two episodes of diverticulitis; however, more recent evidence suggests that morbidity and mortality is not increased after more than two episodes. The American Society of Colon and Rectal Surgeons (ASCRS) recommends that elective surgery should be individualized to each patient, and should take into account the operative risk, the inability to exclude an underlying cancer, and the patient's quality of life [1]. Thus, insight regarding an elevated risk of future recurrences is relevant to making an informed decision. A recent Markov Decision Model concluded that the quality-adjusted survival between colectomy and medical management reaches an equilibrium after a third episode (second recurrence) and favors surgery after any subsequent recurrences [2].

Similarly, the DIRECT trial demonstrated that among patients with three or more episodes of diverticulitis, surgery resulted in an improved short-term and long-term quality of life compared to medical management alone [3, 4]. In our analysis, patients who suffered a first recurrence were 2-fold more likely to experience at least one more recurrence if they had a positive family history. This knowledge could be used to predict patients at risk for multiple recurrences, in whom earlier operative intervention may be beneficial.

We believe that assessing family history for all patients with diverticulitis would be helpful in counselling patients on their risk of recurrence and could potentially change the recommendations for elective surgery, while taking into account other individual risk factors.

References

1. Feingold D, Steele SR, Lee S, Kaiser A, Boushey R, Buie WD, Rafferty JF. Practice parameters for the tretament of sigmoid diverticulitis. Dis Colon Rectum. 2014;57:284-94.

2. Andeweg CS, Groenewoud J, van der Wilt GJ, van Goor H, Bleichrodt RP. A Markov Decision Model to guide treatment of recurrent colonic diverticulitis. Clin Gastroenterol Hepatol. 2016;14:87-95.

3. van de Wall BJM, Stam MAW, Draaisma WA, Stellato R, Bemelman WA, Boermeester MA, Broeders IAMJ, Belgers EJ, Toorenvliet BR, Prins HA, Consten ECJ; DIRECT trial collaborators. Surgery versus conservative management for recurrent and ongoing left-sided diverticulitis (DIRECT trial): an open-label, multicentre, randomised controlled trial. Lancet Gastroenterol Hepatol. 2017;2:13-22.

4. Bolkenstein HE, Consten ECJ, van der Palen J, van de Wall BJM, Broeders IAMJ, Bemelman WA, Lange JF, Boermeester MA, Draaisma WA; Dutch Diverticular Disease (3D) Collaborative Study Group. Long-term outcome of surgery versus conservative management for recurrent and ongoing complaints after an episode of diverticulitis: 5-year follow-up results of a multicenter randomized controlled trial. Ann Surg. 2019;269:612-20.