A Population-Based Analysis of the Clinical Course of Colonic Diverticulitis and its Evolving Management

by

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A thesis submitted in conformity with the requirements for the degree of Masters of Science, Clinical Epidemiology and Health Care Research
Institute of Health Policy, Management, and Evaluation
University of Toronto

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Abstract

Evidence has accrued to support change in the management of colonic diverticulitis. Advances in imaging and medical management suggest more patients may be managed non-operatively; while various new operative approaches have been proposed as an alternative to Hartmann’s procedure when urgent surgery is necessary. Furthermore, published reports suggest the clinical course of the disease may be characteristically benign; suggesting interval elective colectomy may be unnecessary for the majority of patients, even those with known risk factors.

Reports to date consist predominantly of institutional cohort studies with high loss to follow-up and failure to account for competing risks. To address the gaps in knowledge, we performed a population-based retrospective cohort study. The objectives of this study were to (a) evaluate temporal trends in the management of diverticulitis, and (b) characterize the clinical course of the disease following initial non-operative management. Results from this study will help to inform best practice recommendations.
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Chapter 1
Background & Objectives

1.1 Pathophysiology of diverticular disease

Colonic diverticulosis is defined by the presence of diverticula, which are sac-like protrusions of mucosa and submucosa layers within the large intestine. Diverticula most often develop at areas of relative weakness in the bowel wall, where blood vessels (vasa recta) penetrate the muscle layer of the intestine to reach the mucosa and submucosa. It has been hypothesized that diverticula have a propensity to develop within the large intestine because unlike the small intestine, the wall of the colon contains only a single layer of circular muscle, the outer longitudinal muscle layer being divided into bands of taenia coli.

The pathogenesis of colonic diverticula remains poorly understood, but studies have demonstrated an association between colonic diverticula and abnormal intestinal motility, diet, and genetics. Low intake of fiber in the diet may result in less bulky stools that retain less water, which may alter gastrointestinal transit time and colonic motility, working to increase intraluminal pressure and resulting in herniation of mucosa and submucosa. Consistent with this, prolonged transit time, small stool volumes, and increased intraluminal pressure have been observed to be associated with increased risk of diverticular disease. Abnormalities of the wall structures may also contribute to development of diverticula, as patients with connective
tissue disorders such as Ehlers-Danlos and Marfan's syndromes are observed to develop the condition at a younger age\textsuperscript{2}.

The presence of diverticula typically remains asymptomatic until the development of bleeding or infection occurs. In fact, approximately 75-85\% of patients with diverticula are believed to remain asymptomatic\textsuperscript{1,11}. The clinical spectrum of symptomatic diverticular disease is variable, and ranges from episodic pain, to simple uncomplicated diverticulitis, to life-threatening complicated disease such as perforation or hemorrhage. Gastrointestinal bleeding can occur due to the presence of diverticula, as the penetrating blood vessel at the site of the diverticulum can be injured and weakened over time, predisposing to leakage of the blood vessel. Bleeding occurs in approximately 5\% to 15\% of patients with diverticulosis, whereas severe life-threatening bleeding has been found to occur in 3\% of patients with diverticulosis\textsuperscript{12}. Diverticular bleeding is often self-limiting, but may require intervention such as embolization and emergency colectomy.

In contrast to diverticulosis, diverticulitis is characterized by the presence of inflammation within the diverticulum, which is often accompanied by micro or macro perforation. The process by which diverticula become inflamed to result in diverticulitis remains unknown. Early theories of diverticulitis pathophysiology focused on stasis or obstruction by fecolith or food particles, followed by bacterial overgrowth, increased pressure and local tissue ischemia\textsuperscript{4}, until micro- or macro-perforation results. More recently, it has been postulated that abnormal intestinal motility in conjunction with abnormal colonic flora or microenvironment may contribute to the development of diverticulitis\textsuperscript{2,3}, although the exact mechanisms remain unclear.
1.2 Epidemiology of diverticular disease

The true prevalence of colonic diverticula is unknown, as the majority of patients remain asymptomatic. One observational study of over 9000 patients who underwent colonoscopy demonstrated an overall prevalence of 27%\textsuperscript{13}. The prevalence of colonic diverticula is known to increase with age. Diverticula have been found to be present in less than 10% of patients younger than 40 years of age, increasing to as many as 65% of the population over 85 years of age\textsuperscript{4, 7, 13-18}.

The prevalence and location of the diverticula have been found to vary by geography\textsuperscript{19}. The highest prevalence of colonic diverticula have been reported in industrialized western countries (Europe, United States, Australia), where 50% of the population over 60 years of age have diverticulosis\textsuperscript{14}, and much lower prevalence have been reported in Asian and African populations\textsuperscript{14, 19, 20}. The Western diet, being low in fiber and high in fat, has been hypothesized to be a causative factor in the geographical differences. There is evidence that the rates of symptomatic diverticular disease have been rising in developing countries as they adopt a more Western diet and lifestyle\textsuperscript{21, 22}. In addition to geographical differences in the prevalence of diverticula, there are also geographical differences in the location of colonic diverticula when present. Diverticula are more commonly located in the left colon in Western Countries, with over 90% of cases being located in the sigmoid and descending colon\textsuperscript{23}. By contrast, the disease is more commonly right-sided in Asian populations\textsuperscript{14, 19, 24, 25}, and reports suggest complications from right sided diverticulosis appear to be less frequent than left-sided diverticulosis\textsuperscript{26}.

Acute diverticulitis has traditionally been thought to develop in as many as 10-25% of patients with colonic diverticulosis\textsuperscript{2, 15}. However, one report evaluating over 2000 patients with
diverticulosis noted on colonoscopy found that only 4.3% of patients developed diverticulitis over an 11 year follow-up period\textsuperscript{27}. In the United Kingdom, the rate of hospital admissions for diverticulitis is 23/100,000 per year for males and 32/100,000 per year for females\textsuperscript{28}. The rate of perforation of large bowel diverticula is low however, estimated at 4.0 cases per 100,000 per year, with the risk estimated to be higher in men than women (5.8 vs 3.1)\textsuperscript{29}. Diverticulitis represents a significant cause of morbidity and healthcare resource burden. The disease accounts for more than 300,000 hospitalizations annually in the US\textsuperscript{30}, at an estimated cost in excess of $2.4 billion\textsuperscript{31}. In the province of Ontario, Canada, there were 133,875 admissions for diverticular disease between 1998 and 2001\textsuperscript{32}. Furthermore, the incidence of diverticulitis has been increasing over the past decade\textsuperscript{33, 34}. A study of hospitalizations in the United States showed an increase in admissions for acute diverticulitis from 1998 to 2005, with the largest increase being found in younger patients age 18 to 44\textsuperscript{33}. The rise in diverticulitis incidence in younger patients has been observed in several reports\textsuperscript{28, 32, 35, 36}, and may be related to increasing obesity rates in the younger population\textsuperscript{37}.

Sex differences in the incidence of diverticular disease have been noted. The condition appears to be more common in men for the population under age 50 years, but the incidence is higher in females for the population older than 50 years of age\textsuperscript{7, 32}. Lifestyle factors have been found to be associated with the development of diverticular disease. Low dietary fiber intake has been hypothesized to predispose to development of colonic diverticula\textsuperscript{7, 8, 38, 39}. In one large prospective cohort study, dietary fiber intake was found to be associated with reduced risk of developing diverticular disease, with a relative risk (RR) of 0.58 (95% confidence interval 0.41-0.83)\textsuperscript{39}. High intake of dietary fats and red meat has also been shown to be associated with increased risk of the disease\textsuperscript{40}. Conversely, physical activity is associated with reduced risk of
diverticulitis and diverticular bleeding\textsuperscript{41, 42}, whereas obesity is associated with increased risk\textsuperscript{43-46}. Smoking appears to be associated with increased risk diverticular disease as well as the risk of perforated disease and abscess formation\textsuperscript{47}. Medications such as steroids, non-steroidal anti-inflammatory drugs, and opiates have been associated with increased risk of complications and bowel perforation from diverticulitis\textsuperscript{48-51}.

1.3 Diagnosis and Management of Acute Diverticulitis

1.3.1 Diagnosis of acute diverticulitis

The clinical presentation of acute diverticulitis typically comprises of abdominal pain and fever. Other common symptoms include nausea, vomiting, and constipation or diarrhea\textsuperscript{1}. The initial evaluation of a patients with suspected acute diverticulitis should include a history and physical examination, and complete blood count\textsuperscript{52}. Laboratory studies often reveal leukocytosis. Computed tomography (CT) with intravenous and oral contrast administration is the most appropriate imaging modality to confirm the diagnosis\textsuperscript{52, 53}. CT has the ability to diagnosis diverticulitis as well as the ability to diagnose or exclude other disease processes that may present like diverticulitis. The sensitivity of computed tomography in diagnosing diverticulitis is high, estimated at 93-97\%, and specificity approaches 99\%\textsuperscript{54-56}. Furthermore, computed tomography has been shown to accurately predict medical treatment failure based on the radiologic severity of the disease\textsuperscript{57}. Endoscopic evaluation is contraindicated in the acute setting due to the increased risk of colonic perforation in the setting of inflammation, unless inflammatory bowel disease, ischemic colitis or carcinoma are highly suspected\textsuperscript{1}. Colonoscopy is commonly recommended 6-8 weeks following the recovery to exclude carcinoma, although the
necessity of routine colonoscopy for patients diagnosed with uncomplicated diverticulitis on computed tomography has been questioned\textsuperscript{58-61}.

The clinical spectrum of the disease varies from mild inflammation and discomfort to free perforation and septic shock. The disease is commonly described as uncomplicated or complicated, based upon clinical severity and findings on diagnostic imaging. Uncomplicated diverticulitis makes up over 75\% of cases of the disease, whereas up to 25\% of patients may suffer complications such as abscess, fistula, or free perforation\textsuperscript{31}. Small perforations are often walled off by pericolic fat, mesentery, or omentum, which may result in a simple localized inflammation, phlegmon, or abscess. An estimated 17\% of patients with diverticulitis present with abscess, although the risk of developing an abscess associated with diverticulitis is estimated to range from 10\% to 24\% depending on age\textsuperscript{62,63}. Abscess formation associated with diverticulitis has been observed to carry a mortality risk of 6\%\textsuperscript{64}. If this process erodes into adjacent structures, fistula may form. The risk of fistula formation secondary to diverticulitis was found to be 0.7\% of younger patients and 2.2\% of older patients with a primary episode of diverticulitis\textsuperscript{65}, and most commonly occur within the bladder, although fistulae may also develop between the colon and small bowel, vagina, and skin. In the long term, stricture formation secondary to inflammation and infection can lead to bowel obstruction.

In contrast, inability to contain the perforated diverticulum or abscess results in free perforation of pus or feces, resulting in generalized peritonitis and need for urgent operative intervention. When urgent operation is required, it is associated with high morbidity and mortality, with the reported morbidity rate estimated at up to 56\% and mortality rates in the range of 9-29\% in published reports\textsuperscript{66-70}, varying by severity of disease. In large multi-institutional cohort studies, the observed mortality rate associated with operation for complicated
diverticulitis or perforated diverticulitis was 12%\textsuperscript{68,71}. A recent meta-analysis comparing operative strategies for perforated diverticulitis and including 15 studies and 963 patients reported an overall mortality risk for such patients to be 5-15%\textsuperscript{72}.

The most widely used classification system for disease severity is the Hinchey\textsuperscript{73} or modified Hinchey classification, which is based on diagnostic imaging findings\textsuperscript{57,74,75}. Stage I diverticulitis is defined by the presence of pericolic or mesenteric abscess, stage II is defined by pelvic abscess, and stages III and IV are defined as generalized purulent and feculent peritonitis respectively.

1.3.2 Non-operative management of acute diverticulitis

Severity of the disease episode, as determined by clinical evaluation and radiologic findings, as well as the underlying health of the patient, determines the best treatment for diverticulitis. Treatment guidelines have been published by various national societies\textsuperscript{52,53,76,77}. Conservative treatment consisting of bowel rest and antibiotics is usually effective in treating mild disease (Hinchey I)\textsuperscript{4}. While antibiotics continue to be the mainstay of treatment, the benefit of antibiotics in treating uncomplicated diverticulitis has been questioned and remains unclear\textsuperscript{78,79}. Hjern et al\textsuperscript{80} reported that 186 of 193 patients with CT-proven non-perforated diverticulitis experienced resolution of the disease episode without antibiotics, and a Cochrane review suggests there may be no significant difference between antibiotics and no antibiotics for the treatment of uncomplicated diverticulitis\textsuperscript{78}. This suggests uncomplicated diverticulitis may be a self-limiting process. Currently there is insufficient evidence to conclude that patients with uncomplicated diverticulitis can be safely managed without antibiotics, so it continues to be the mainstay of treatment in uncomplicated disease.
Most patients with uncomplicated diverticulitis who are clinically stable and able to tolerate oral fluids are able to be successfully treated in the out-patient setting. Mizuki et al\textsuperscript{81} demonstrated that 68 of 70 patients with Hinchey I and II disease were successfully managed without admission. For such patients, 7-10 days of oral broad-spectrum antimicrobial therapy is often prescribed, including coverage against anaerobic organisms. A low-residue or liquid diet is commonly prescribed, although evidence for such dietary recommendations are limited\textsuperscript{82}. The decision to admit a patient to hospital is made based on clinical status at presentation and severity of disease based on diagnostic imaging. Hospitalization and administration of intravenous fluids and antibiotics should be considered when patients have complicated disease, are unable to tolerate oral fluids, or have significant medical comorbidities\textsuperscript{1}. Patients who are elderly, immunosuppressed, or diabetic may be best managed as in-patients as evidence suggests they are more likely to fail medical management\textsuperscript{83} and are more likely to experience complications such as perforation and abscess formation\textsuperscript{84}. If there is no improvement in pain, fever or leukocytosis within 2-3 days of medical management, repeat imaging with computed tomography is warranted to rule out development of complicated disease.

Patients with Hinchey II diverticulitis are often treated by antibiotics and image-guided percutaneous abscess drainage\textsuperscript{52, 53}. Small abscesses (less than 3-4 cm in size) are often successfully managed with antibiotics alone, whereas larger abscesses often require drainage\textsuperscript{4, 14, 52, 57, 85}. Patients who fail to improve on medical management and percutaneous abscess drainage should undergo urgent operative intervention. Large abscesses and patients with pelvic abscesses are more likely to require surgery than small mesocolic abscesses\textsuperscript{86}. 
1.3.3 Indications for urgent operative intervention

Although most cases of acute diverticulitis can be successfully managed non-operatively, cases not responding to medical management and those with uncontrolled sepsis, uncontained perforation, or generalized peritonitis will require emergency operation. In observational studies, about 15-20% of patients admitted for diverticulitis undergo urgent operative intervention. There is evidence to suggest urgent operations for acute diverticulitis are becoming less common, while the use of percutaneous drainage has been increasing. For example, Salem et al performed a retrospective cohort study which utilized data from a statewide administrative database, including 25,058 patients hospitalized non-electively with diverticulitis from 1987 to 2001. The authors of this study found that the odds of an emergency colectomy at initial hospitalization decreased by 2% per year (OR 0.98, 95% CI: 0.98-0.99), while the odds of percutaneous abscess drainage increased 7% per year (OR 1.07, 95% CI: 1.05-1.10). Such findings may be related to increasing success in managing complicated diverticulitis using non-operative treatment strategies. For example, Dharmarajan et al reported 136 cases of diverticulitis with extraluminal air, fluid and/or abscess and only 5 required urgent operation. Of the remaining 131 patients who were managed non-operatively, 28% required percutaneous abscess drainage and only 7 (5%) failed medical/percutaneous management and required urgent operation. Of the 27 patients with air remote from the perforation site, 25 (93%) were successfully managed medically. Similarly, Sallinen et al reported on a retrospective review of all patients with CT-diagnosed acute perforated diverticulitis with extra-luminal air from 2006 - 2010. In this cohort, 48 of 180 patients underwent urgent surgery at admission, and 132 of 180 patients were managed non-operatively. The authors of this report observed that of patients with
pericolic air (n = 82) without abscess, non-operative management was successful in 99% of cases with 0% mortality. Of patients with distant free air (n = 29), non-operative management was successful in 62% of cases, with 0% mortality. Reports such as the ones discussed above suggest that many patients with complicated diverticulitis who are clinically stable without signs of sepsis or peritonitis may be successfully managed medically.

1.3.4 Urgent operative management strategies for acute diverticulitis

Urgent operative strategies in the setting of acute diverticulitis have evolved significantly over the past decade. Hartmann’s procedure, consisting of a two-stage procedure consisting of laparotomy, resection of the diseased segment with end colostomy and rectal stump, and potentially followed by subsequent colostomy reversal to restore bowel continuity, has been the operation of choice for acute complicated sigmoid diverticulitis since the 1980’s \(^92,93\). However, over the past decade, primary anastomosis, with or without diverting ileostomy, as well as various laparoscopic and non-resection approaches have gained increasing attention and popularity in the urgent operative treatment of acute diverticulitis.

**Hartmann’s procedure versus primary anastomosis**

Hartmann’s procedure has traditionally been the procedure of choice for complicated, perforated diverticulitis. However, this procedure is associated with significant morbidity from complications and a perioperative mortality rate of 15% \(^72\). Furthermore, reversal of Hartmann’s procedure to restore bowel continuity is itself a morbid and technically challenging procedure, with surgical and medical complication rates reported to be 44% and 9% respectively, with a mortality rate of 1.7% \(^94\). Subsequently, it has been observed that only 56% of patients receiving
Hartmann’s procedure undergo subsequent operation to restore bowel continuity, resulting in a decrease in quality of life and sexual functioning associated with having a permanent colostomy.

For these reasons, primary resection and anastomosis, with or without diverting loop ileostomy, has been advocated as an alternative to Hartmann’s procedure for patients with complicated, perforated diverticulitis. While the inclusion of a diverting ileostomy necessitates a two-stage operation, the morbidity associated with ileostomy closure is lower than Hartmann’s reversal, thereby increasing the likelihood of restoration of bowel continuity. Results from observational studies suggest primary anastomosis with and without diverting loop ileostomy is a safe alternative to Hartmann’s procedure for complicated diverticulitis in selected patients, with similar morbidity and mortality. In one systematic review of observational studies, the leak rate for primary anastomosis and proximal diversion in appropriately selected patients was low at approximately 6%. A recent systematic review of 15 studies including 963 patients reported a significantly reduced mortality rate for primary anastomosis compared to Hartmann’s procedure (4.9% versus 15.1%).

Few randomized trials have been published to evaluate the safety of primary anastomosis in the setting of acute complicated diverticulitis. In one multicenter trial, Oberkofler et al. randomized 62 patients with Hinchey III and IV diverticulitis to either primary anastomosis with diverting ileostomy or Hartmann’s procedure, and found no significant differences in mortality and morbidity between the two groups during the initial operation. However, patients randomized to primary anastomosis with diverting ileostomy were more likely to undergo reversal of their ostomy (90% versus 57%, p<0.001), with fewer complications during ostomy closure, shorter operating time, shorter hospital stay, and lower in-hospital costs. The trial was terminated early after an interim analysis reported significant differences in outcome favoring
primary anastomosis. Of note however, the trial was limited by small sample size and potential biases related to surgeon influence over the randomization process.\textsuperscript{108}

The observational nature of the data available to date precludes us from concluding that primary anastomosis is safe for all patients with perforated diverticulitis. Selection bias in these observational studies makes it difficult to extend conclusions to all patients with complicated diverticulitis. In fact, in one large observational study using data from the National Surgical Quality Improvement Program (NSQIP), primary anastomosis with proximal diversion was associated with twofold greater mortality risk than Hartmann’s procedure when analyzing the highest risk patients, those with cases classified as dirty or infected.\textsuperscript{102} Furthermore, while the leak rate was found to be low in well-selected patient cohorts, other reports have observed the leak rate for primary anastomosis without diverting ileostomy to be as high as 28%.\textsuperscript{109} Taken together, the evidence suggests that while patients with frank perforation and hemodynamic instability are poor candidates, there remains a select subset of low-risk patients who may benefit from primary anastomosis, but it remains unclear which patients are best suited for primary anastomosis versus Hartmann’s procedure. The decision to perform primary anastomosis is based on clinical judgment of the patient’s risk profile, including consideration of the amount of bowel contamination, the patients’ clinical status, medical comorbidities, nutritional status and quality of the tissues.\textsuperscript{4} The role and safety of primary anastomosis, particularly without diverting ileostomy, remains unclear.\textsuperscript{53} results from ongoing trials may add new knowledge to better inform choice of operative strategies in treating perforated diverticulitis.\textsuperscript{107}

**Non-resectional & laparoscopic strategies in emergency diverticulitis surgery**
More recently alternative options have been proposed, including the use of non-resectional operative strategies such as laparoscopic lavage and drainage, as well as use of laparoscopic colon resection and laparoscopic Hartmann’s procedure\textsuperscript{110}.

Laparoscopic peritoneal lavage (or laparoscopic “washout”) has gained attention as an alternative to colonic resection for patients with complicated diverticulitis and purulent peritonitis, but does not apply to patients with frank feculent peritonitis. The goal is to contain contamination and drain infection, allowing patients with Hinchey stage III disease to avoid urgent resection and ostomy. This is often performed as a bridge to elective colectomy, although some advocate that subsequent elective colectomy may not be necessary. Observational studies have demonstrated laparoscopic lavage to be successful in a large majority of patients, with low morbidity and mortality\textsuperscript{111-114}. Myers et al\textsuperscript{113} performed a prospective multi-institutional study evaluating the outcomes associated with laparoscopic lavage. Of 100 patients with perforated diverticulitis and generalized peritonitis, 92 patients were managed by laparoscopic lavage. The authors report a low morbidity and mortality rate of 4\% and 3\% respectively; with only 2 of the 92 patients requiring further intervention (one required a percutaneous abscess drain and the other failed treatment and required a Hartmann’s procedure). A recent systematic review of 12 non-randomized studies including 301 patients demonstrated that laparoscopic lavage was associated with low conversion rates (4.9\%), a mean complication rate of 18.9\%, and a low overall mortality rate of 0.25\%\textsuperscript{115}. Although laparoscopic lavage has gained attention as a potential non-resectional strategy in treating Hinchey III disease, there is currently no level I evidence to support its use. Further randomized trials are needed to inform the use of this operative strategy, identification of patients who are at increased risk of failure from laparoscopic lavage will be important\textsuperscript{107,116}.
Laparoscopic colon resection for diverticular disease has been shown to provide benefits over open surgery in the elective setting, including a decrease in postoperative pain, complications, ileus, and shorter length of hospital admission compared to open operative approaches. However, the role of laparoscopy in the urgent setting for acute complicated diverticulitis has not been well studied. There has been limited use of laparoscopic colectomy and laparoscopic Hartmann’s procedure in the emergency setting, making up only 2.8%–7.8% of urgent operations in the literature. Masoomi et al reported increasing use of laparoscopy in both elective and urgent surgery for diverticulitis. There is limited data on the safety and efficacy of laparoscopy in emergency diverticulitis surgery. In one large retrospective study, the American College of Surgeons-National Surgical Quality Improvement Program (ACS-NSQIP) database was used to compare outcomes for patients with diverticulitis who underwent surgery by open versus laparoscopic approach. Of the cohort of 11,981 patients, 1,946 (16%) cases were categorized as emergent, of which only 138 (7.1%) were performed laparoscopically (consisting of laparoscopic primary anastomosis and laparoscopic colostomy), and the remaining 1,808 (92.9%) were performed open. The authors of this study performed a multivariate logistic regression to compare morbidity and mortality of open versus laparoscopic approaches. Although limited by selection bias, risk-adjusted analysis of outcomes comparing laparoscopic to open approaches for emergency diverticulitis cases demonstrated no significant difference in mortality, overall complications, sepsis, or wound infections. Laparoscopic surgery in the emergency setting was associated with reduced odds of respiratory complications postoperatively (OR 0.37, 95% confidence interval 0.15–0.88).

In another large observational study using NSQIP data from 2005 to 2009, Turley and colleagues used a propensity matched analysis to compare outcomes of laparoscopic versus open
Hartmann’s procedure in the emergency setting for patients with colonic diverticulitis\textsuperscript{120}. In unadjusted comparisons, the laparoscopic group experienced fewer overall complications (26\% vs 42\%, \( p=0.008 \)), and shorter length of stay in hospital (8.9 days vs 11.6 days, \( p<0.001 \)), with no difference in operative times. However, after controlling for confounders using propensity score matching, the laparoscopic approach was not found to be associated with any decrease in morbidity or mortality.

The use of laparoscopy in the emergency setting for complicated diverticulitis remains controversial; not only does the presence of acute inflammatory adhesions and phlegmon make a laparoscopic approach more challenging technically, there are also concerns of extending the operating time for patients who are acutely ill and septic. The results from these observational studies suggest that the benefits of laparoscopy seen in elective colon resection may not apply in emergency cases. However, potential benefits such as postoperative pain, ileus, length of stay and readmissions have not been well studied, which represent important clinical outcomes that may favor laparoscopy. Further research is needed before conclusions of safety and efficacy can be drawn, and before more surgeons will be comfortable utilizing this approach in the emergency setting.

\subsection{1.4 Clinical Course of Diverticulitis}

The natural history of the disease can be studied through evaluation of the long term outcomes of patients who are managed non-operatively at the initial diagnosis of diverticulitis. Reports to date have consisted predominantly of case series and small cohort studies with high loss to follow-up. Reported disease recurrence rates initially ranged from 17\% to 48\% for patients managed non-operatively\textsuperscript{15, 57, 65, 67, 121-127}. More recently, large cohort studies have
emerged to better characterize the clinical course of the disease\textsuperscript{87, 88, 126, 128, 129}. These reports suggest the natural history of diverticular disease may be more benign than previously thought, with few patients experiencing further disease-related adverse events in the long term. For example, Broderick-Villa et al reported that 86% of patients managed non-operatively for an episode of diverticulitis requiring admission had no further admissions for diverticulitis over 8.9 years of follow-up. Recurrence occurred in 13.3% of the patients and only 3.9% had a re-recurrence. In multiple reports, complicated recurrence was experienced by only 2.1%-5.0% of the patients with initial uncomplicated disease that was managed non-operatively\textsuperscript{123, 127, 128}. Overall, the risk of recurrence for patients with simple uncomplicated index disease appears to be in the range of 10% to 35%\textsuperscript{87, 88, 123, 127, 129, 130}, whereas the reported risk of emergency operation have ranged from 1.4%-8.3%\textsuperscript{88, 126-129}.

These observational studies imply that conservative non-operative treatment may be appropriate for the majority of patients who have an episode of uncomplicated diverticulitis managed non-operatively, and that elective colectomy may be unnecessary for most. Current practice guidelines reflect these findings, elective colectomy is not recommended for patients who have had an episode of uncomplicated diverticulitis managed non-operatively\textsuperscript{52}. However, there is little evidence to guide the recommendation of elective colectomy for patients who have traditionally been considered at high risk for further disease events, including: (a) patients younger than 50 years at first disease presentation, (b) patients who have had an episode of complicated disease such as abscess requiring percutaneous abscess drainage, and (c) patients who have had multiple disease episodes managed non-operatively. These factors have traditionally been thought to infer greater risk of disease recurrence and more virulent disease trajectory requiring emergency operation\textsuperscript{4, 53, 131}, which has prompted authors of practice
guidelines to recommend elective colectomy for such high risk patients\textsuperscript{52, 53, 131}. Over the past decade however, there is increasing evidence to challenge these recommendations.

**Young age**

Studies evaluating the disease trajectory for patients less than 50 years of age at first presentation have reported mixed results. Some studies have reported a risk towards greater severity of disease and complications \textsuperscript{16, 37, 62, 132, 133}, as well as greater risk of disease recurrence following successful non-operative management \textsuperscript{36, 62, 63, 87, 126, 132, 134}, while other reports have not observed any greater risk of recurrence or complications in young patients\textsuperscript{57, 62, 125, 126, 135-139}. For example, in one large population –based retrospective cohort study, only 7.5% of young patients subsequently required emergency operation for diverticulitis following recovery from an initial episode of diverticulitis\textsuperscript{129}. Other retrospective studies have estimated this risk to be even lower at 2.1\textsuperscript{140}. In one retrospective review of patients under age 50 with diverticular disease, only 1 out of 196 medically managed patients experienced subsequent perforation during a median follow-up of 5 years\textsuperscript{136}. Furthermore, even if younger patients are at increased risk of subsequent emergency operation, the absolute risk difference is likely to be low\textsuperscript{129, 141}, and the clinical difference may be minimal. For example, the absolute risk difference was only 2.5% in one large population based study (7.5% vs 5%), resulting in needing to treat 13 young patients with elective surgery to prevent one emergency operation\textsuperscript{129}.

To address this question, two recent meta-analyses have been published comparing the clinical course for patients younger and older than age 50\textsuperscript{141, 142}. While both studies observed young age to be associated with increased risk of readmission (pooled relative risk: 1.7), they differed in their conclusions regarding the relative risk of subsequent emergency operation for younger patients. Van de Wall et al\textsuperscript{141} included 8 cohort studies comparing patients younger
and older than 50 years of age with diverticulitis; the authors demonstrated young patients have higher risk of recurrent disease (pooled RR 1.73, 95% CI: 1.40-2.13). The estimated average cumulative risk of readmission for young patients was 30% in this study, compared to 17% for patients over age 50. In this study, young patients were not found to be at higher risk of requiring urgent surgery during the index hospitalization (RR 0.99, 95% CI: 0.74-1.32), but young patients did appear to be at increased risk of requiring urgent surgery during hospitalizations for recurrent episodes (pooled RR 1.46, 95% CI: 1.29-1.66). However, despite the higher relative risk, the absolute risk difference was small (7.3% vs 4.9%). By comparison, Katz et al\textsuperscript{142} also found that young patients were more likely to experience recurrence (RR 1.70, 95% CI: 1.31-2.21), with the recurrence rate estimated to be 31.6% in young patients compared to 18.5% in patients older than 50 years. However, Katz et al demonstrated no increased risk of urgent operation for young patients (RR 0.69, 95% CI: 0.46-1.06). At present, it is unclear if young age at first presentation confers greater risk of requiring emergency operation.

**Complicated disease**

Complicated diverticulitis accounts for 20-30% of cases of diverticulitis\textsuperscript{28,31}, yet little is known about the natural history of the disease following an episode of complicated diverticulitis. In retrospective reports, the majority of patients who require percutaneous drainage of abscess for diverticulitis have undergone elective colectomy following discharge\textsuperscript{143}. Recommendation for elective interval colectomy have been made in response to observations of increased risk of disease recurrence and emergency operation for patients with complicated disease than those with uncomplicated diverticulitis\textsuperscript{52,53,57,86}. Few studies have reported the clinical course of patients following non-operative treatment of complicated diverticulitis, reports to date consist of
small case series and cohort studies, with recurrence rates reported to be as high as 50-70%\textsuperscript{57, 86, 87, 144-146}.

The practice of routine elective interval colectomy for patients with complicated disease has recently come under question\textsuperscript{143}, as the recurrence and emergency surgery risk following complicated disease managed non-operatively remains poorly understood, and large prospective data remains lacking. Whereas elective resection is generally indicated for patients with disease complicated by stricture or fistula formation, the role of surgery is less well defined for patients who have experienced abscess formation successfully managed non-operatively and who no longer experience ongoing symptoms from the disease. Percutaneous drainage has traditionally been recommended to treat larger abscesses associated with acute diverticulitis as a bridge towards elective interval colectomy, allowing the patient to have an elective single stage procedure, with reduced risk of morbidity and stoma creation\textsuperscript{147}.

However, there is now some evidence to suggest that percutaneous drainage may be sufficient treatment alone, without elective colectomy after the acute inflammation settles, but this has been limited to small cohorts with high loss to follow-up\textsuperscript{57, 64, 86, 124, 143, 148-152}. Updated reports have demonstrated the recurrence rate following non-operative management of complicated diverticulitis to be in the range of 24\% to 53\%\textsuperscript{15, 57, 127, 143, 148}, although the risk of colonic fistula development following percutaneous abscess drainage for complicated diverticulitis may be as high as 47\%\textsuperscript{147}. The size and location of abscesses may be an important determining factor in long term outcomes. Ambrosetti et al demonstrated that pelvic abscesses were associated with greater risk of subsequent surgery than abscesses located above the pelvic brim\textsuperscript{86}, and abscess size >5 cm was associated with increased risk of disease recurrence\textsuperscript{143}. Felder et al found that patient comorbidities, such as immunosuppression and renal insufficiency,
may predict the need for urgent colectomy following percutaneous drainage. Further research is needed to accurately characterize the long term risks of recurrence and emergency surgery following non-operative treatment of complicated diverticulitis, to better inform decisions regarding elective interval colectomy for this subgroup of patients.

**Recurrent disease episodes**

Recurrent diverticulitis has traditionally been considered an indication for interval elective colectomy. This recommendation dates back to reports by Parks in the 1960’s observing subsequent episodes of diverticulitis were less likely to respond to medical therapy, suggesting that recurrent diverticulitis followed a more aggressive course. This was supported by more recent studies suggesting the number of disease episodes is associated with increased risk of further disease recurrence as well as possibly increased risk of requiring emergency operation. One study observed the risk of re-recurrence to be higher than the risk of first recurrence (29% vs 13%, p<0.001). One large population-based study demonstrated each readmission carried a HR of 2.2 of undergoing emergency operation compared to the admission preceding it.

In contrast, other reports have challenged the hypothesis that recurrent attacks predispose to increased disease mortality and morbidity, suggesting that diverticulitis may not be a progressive disease as previously believed. Studies have shown the risk of complicated recurrence may be as low as 5% in those patients with uncomplicated index disease. In fact, the greatest risk of experiencing complicated disease requiring emergency operation may to be at the index episode, and often represents the first manifestation of the disease. Published observational reports have resulted in an evolution of national guidelines, the recommendation to undergo elective colectomy is no longer based on the number of disease
episodes experienced\textsuperscript{52, 53, 158}. Although there has been no consensus on the number of attacks that prompts elective colectomy, decision analysis has been used to determine the optimal number of recurrences before elective surgery should be performed. In one study, elective colectomy was found to be most cost effective when performed after 3 episodes \textsuperscript{159}, whereas Salem et al found it most cost effective to perform elective colectomy after the 4\textsuperscript{th} disease episode \textsuperscript{160}. However, it is unclear how quality of life is affected by such management strategies when compared to earlier use of colectomy for recurrent disease. Further studies are needed to determine if patients with recurrent attacks are best served with continued conservative management or early elective resection.

1.5 Interval Elective Colectomy

1.5.1 Elective colectomy following diverticulitis

Interval elective colectomy is offered to patients who have had an episode of diverticulitis managed non-operatively, and who either have complications or persistent symptoms from the disease (fistula, obstruction, chronic smoldering diverticulitis), or who are deemed to be at high risk of experiencing subsequent recurrences and need for emergency operation (young age, complicated index disease, multiple recurrent episodes). However, elective colectomy for diverticular disease comes with operative risks that must be weighed against its potential benefits. It is associated with a mortality rate of 0-4\% and morbidity rate of up to 22-30\%.\textsuperscript{67, 161-167} Furthermore, up to 15\% of patients undergoing elective colectomy for diverticular disease may receive an ostomy\textsuperscript{129}. In fact, elective colon resection for diverticular disease has been observed to carry a greater morbidity and mortality than colon resection for cancer \textsuperscript{168-170}. After adjusting for other variables, patients with diverticular disease undergoing elective
colectomy were significantly more likely than patients with colon cancer to experience in-hospital mortality (adjusted odds ratio, 1.90; 95% CI, 1.37-2.63; P < .001), to develop a postoperative infection (1.67; 1.48-1.89; P < .001), and to receive an ostomy (1.87; 1.65-2.11; P < .001). Patients with diverticular disease undergoing elective colectomy also had greater hospital costs and longer lengths of stay in hospital. Taken together, this suggests that elective colectomy for diverticular disease is associated with significant risks that must be taken into account when making the decision to offer surgery for a benign disease. Furthermore, many argue that elective resection following successful non-operative treatment of diverticulitis does not decrease disease-related mortality or prevent complications of the disease. It has been estimated that 18 patients would have to undergo elective operation to prevent one emergency surgery, and the risk of postoperative disease recurrence has been shown to range from 5.8% to 8.7%. As many as 20-25% of patients may experience persistent abdominal symptoms after elective colon resection for diverticular disease.

Although there is little evidence to support the use of elective colectomy in preventing disease-related complications, reports do suggest elective surgery may result in significant improvements in quality of life for patients with recurrent diverticulitis or persistent chronic symptoms. Makela et al demonstrated that elective surgery following 2 episodes of uncomplicated disease was associated with lower need for further physician treatment, readmission and LLQ abdominal pain. Additionally, studies supporting early elective colectomy report that increased number of diverticulitis episodes increases conversion rates at time of elective laparoscopic sigmoidectomy, suggesting early surgery may be preferable to increase the odds of successful laparoscopic surgery.
1.5.2 Evolving role of elective surgery for diverticulitis

There is currently no consensus on the indications for elective colectomy following diverticulitis, and it remains unclear which patients truly benefit from elective colon resection. Traditionally, elective colectomy has been indicated after 2 attacks of uncomplicated diverticulitis, after one attack for patients less than 50 years of age at first presentation, and after one attack of complicated disease. However, over the past decade, treatment algorithms have evolved in response to a better understanding of the clinical course of the disease suggesting that the risk of disease recurrence and emergency operation without elective interval colectomy may be lower than previously described\textsuperscript{52,53}, suggesting the majority of patients with diverticulitis do not require interval elective colectomy.

However, despite the recommendations for more selective use of elective colectomy following diverticulitis, the per capita rates of elective surgery for diverticulitis have continued to increase\textsuperscript{33,180}, which may be due to increases in the incidence of the disease and an aging population overall. Between 1998 and 2005, a review of the NIS demonstrated a 38% increase in elective operations for diverticular disease, particularly among young patients. This was accompanied by declines in the rates of operative mortality and length of stay in hospital\textsuperscript{33}. However, the proportion of patients undergoing surgery for uncomplicated diverticulitis decreased from 17.9% to 13.7%\textsuperscript{34}. Further research is needed to determine how the use of elective colectomy for diverticular disease has evolved, and to determine if current practice patterns are reflective of best available evidence and updated management guidelines.
1.6 Gaps in Knowledge & Study Rationale

Diverticulitis is one of the most common reasons for surgical admission in the developed world, and accounts for a significant burden on the healthcare system. Although most patients have an uncomplicated course, a subset will develop severe, progressive, recurrent, or refractory disease leading to peritonitis, life-threatening sepsis, and need for urgent colectomy and/ or colostomy. This unpredictable course has led to the practice of elective colectomy following initial non-operative management in high-risk patients, particularly for those who are younger than 50 years of age at first presentation, patients who have had a complicated episode with abscess or perforation, and those who have had repeated attacks.

In recent years, management strategies have evolved in response to increasing evidence to support more conservative treatment approaches. Uncertainty regarding the long-term risk of adverse disease events has led many to challenge the traditional indications for elective colectomy. However, most reports are from small single cohort studies; few population-based studies have been published to date. Furthermore, existing studies that have failed to account for the presence of competing events, which can lead to an overestimate of adverse disease events.

Without a good understanding of the clinical course of the disease and of the risk factors predisposing to adverse outcomes, it is unclear which patients truly benefit from elective surgery. Overuse of elective colectomy for patients with a history of diverticulitis may result in unnecessary operations, costs and risks. Additionally, it is unclear how management strategies have evolved given increasing evidence to challenge traditional practices in treating this common surgical disease. This study aims to address the remaining knowledge gaps.
1.7 Thesis Objectives

The objectives of this project are:

(1) To evaluate temporal trends in the management of acute diverticulitis, including the use of non-operative management strategies and percutaneous drainage. We also aimed to evaluate changes in the use of various operative approaches when urgent surgery is necessary, including the use of Hartmann’s procedure and laparoscopy.

(2) To determine the clinical course of patients who are managed non-operatively for a first episode of diverticulitis. Specifically, we aimed to characterize the risk of readmission and emergency operation for recurrent diverticulitis following successful non-operative management of a first episode of the disease, and to determine the patient factors associated with increased risk of readmission and emergency operation for recurrent disease. This includes an evaluation of the effects of age of first presentation, severity of the index disease episode, and number of prior admissions.

(3) To characterize clinical outcomes (mortality, risk of ostomy) and temporal trends in the use of elective colectomy following successful non-operative management of a first episode of acute diverticulitis.
Chapter 2
General Methodology

This was a retrospective cohort study using population-based data from the province of Ontario, Canada. Few population-based studies have been published to date characterizing the clinical course of the disease and the evolving strategies in managing diverticulitis\textsuperscript{33, 34, 89, 129, 180}. Furthermore, existing studies evaluating the clinical course of patients following initial non-operative management have not accounted for the presence of competing events, such as death from other causes and elective colectomy. Analysis of a large population-based cohort of patients with diverticulitis is well-suited to address these gaps in knowledge. This study was approved by the Research Ethics Board of Sunnybrook Health Sciences Centre.

This chapter outlines the general methodology used, including a discussion of the administrative databases used in the study, strengths and limitations of such databases, creation of the study cohort, and methods of statistical analysis.

2.1 Data Sources

Data were obtained from population-based administrative health databases from the province of Ontario, Canada. Ontario has a population of over 13 million residents, all of whom receive medically-necessary healthcare though a publically funded universal system (the Ontario Health Insurance Plan, OHIP), paid for by the provincial government. Healthcare utilization is captured within large administrative databases encompassing a broad range of patient demographics,
clinical information, and services provided. Administrative health records include all hospitalizations, day surgeries, emergency rooms visits, physician services billing, as well as patient, provider, and hospital demographics. Records for each individual are linked across time and datasets using an encrypted unique patient identifier. Such datasets provide longitudinal data for a large unselected cohort of patients, capturing a broad range of medical services with minimal loss to follow-up. All administrative databases were maintained and analyzed at the Institute of Clinical Evaluative Sciences (ICES), Toronto, Canada.

The Canadian Institute for Health Information (CIHI) Discharge Abstract Database (DAD) provides demographic, diagnostic, procedural, and discharge information for all hospital admissions in the province, coded by the International Classification of Disease, Tenth Revision-Canada (ICD-10-CA). The data is collected and submitted to CIHI by individual hospitals, using a standardized data abstraction process. Similarly, the National Ambulatory Care Reporting System (NACRS) is also collected by CIHI from individual hospitals, and includes demographic, diagnostic, and discharge information for all ambulatory clinic and emergency department visits in the province.

The Registered Person Database (RPDB) is provided by the Ontario Ministry of Health and Long Term Care, and reports patient demographic information as well as vital statistics (date of birth, date of death) for all residents of Ontario with a valid provincial health card. The Ontario Health Insurance Plan (OHIP) Billing Database contains records of all physician services that were provided and billed for payment to the Ontario Ministry of Health and Long Term Care. Each record provides data on the physician providing the service, the patient and diagnosis, and the specific services provided, using standardized fee codes (OHIP billing codes). The OHIP
Billing Database was used to obtain details about procedures performed for individuals in our cohort, in addition to procedural codes obtained from the DAD during hospitalizations.

2.2 Data Validity

The validity of administrative discharge data has been reviewed and found to be accurate in other populations\textsuperscript{181}. The administrative health databases used in this project have been validated by the Canadian Institute of Health Information\textsuperscript{182}. The accuracy of the Discharge Abstract Database has been demonstrated for a broad range of diagnoses and procedures in a re-abstraction study, evaluating over 14,000 records across 18 hospital sites in the province of Ontario\textsuperscript{182}. Although there was some variability in the accuracy of diagnosis codes across diseases, Juurlink et al reported good accuracy in the most responsible diagnosis coding and very high accuracy in intervention codes within administrative records. Specifically when evaluating the accuracy of the CIHI data in relation to diverticulitis, there was 84% agreement in the diagnosis of diverticulitis, and 97% agreement in intervention codes, when compared to chart abstraction\textsuperscript{182,183}.

2.3 Study Cohort

All Ontario residents 18 years of age or older who were admitted through any Emergency Department with a most responsible diagnosis of acute colonic diverticulitis from April 1, 2002 to March 31, 2012 were considered for study inclusion (identified by the ICD-10-CA diagnosis codes K57.2 and K57.3 in the DAD). To limit the cohort to patients with a first episode of diverticulitis, patients who had any previous hospital admissions or emergency department (ED) visits for colonic diverticulitis were excluded, dating back to the inception of these administrative databases (1988 for hospital admissions, 2000 for ED visits). Patients with
concurrent gastrointestinal bleeding, or any history of colorectal cancer or colectomy were also excluded (for relevant codes, please see Appendix 1), the remaining patients comprised the final study cohort.

Patients from this cohort who were discharged from hospital without operative intervention, and who had at least 30 days of follow-up, comprised the non-operative subgroup of the study cohort. The clinical course of patients who were initially managed non-operatively was determined by following this subgroup of patients forward in time and characterizing the subsequent risk of hospital readmission and emergency surgery for diverticulitis during the follow-up period.

2.4 Patient Covariates

We sought to evaluate the association of age, disease severity, and number of diverticulitis admissions on the risk of experiencing subsequent disease events. Young age at first presentation was defined as age less than 50 years at index admission. Disease severity was classified as uncomplicated index disease (ICD-10-CA diagnosis code K57.3 - diverticulitis of the large intestine without perforation or abscess), complicated disease without percutaneous abscess drainage (ICD-10-CA diagnosis code K57.2 - diverticulitis of the large intestine with perforation or abscess), or complicated disease with percutaneous abscess drainage (ICD-10-CA diagnosis code K57.2 with procedure code for percutaneous abscess drainage). The number of prior admissions was calculated as a sum of the total number of urgent hospital admissions for diverticulitis at the time just prior to urgent or elective surgery or, in those never undergoing surgical treatment, up until the time of death or end of study follow-up. The number of prior admissions was treated as a repeated events variable using a counting process model.
Baseline patient characteristics including sex, medical comorbidity burden, income quintile, rural residency, and calendar year of index admission were included as covariates in multivariable regression analysis. The Deyo adaptation of the Charlson Comorbidity Index (CCI) was used to represent patient medical comorbidity, calculated from hospital admission records in the one year prior to index admission. Income quintile at the time of index admission was calculated using median neighborhood household income by postal code and Canadian census data. Residency was classified as urban or rural based on postal code, with urban residency being defined as residing within a Census Metropolitan Area or Census Agglomeration with an urban core > 10,000 people (Statistics Canada).

2.5 Outcomes and follow-up

In objective #1, temporal trends in the management of acute diverticulitis are evaluated. The outcomes of interest are trends in the use of various non-operative and operative management strategies. A patient was deemed to have had an operative intervention if there was a concurrent ICD-10-CA procedure code for colectomy, colostomy, diagnostic laparoscopy or laparotomy, or operative (non-percutaneous) abscess drainage during the hospital admission (for relevant codes, see Appendix). The specific management strategies (percutaneous abscess drainage, laparoscopy, Hartmann’s procedure) and the time from hospital admission to operative intervention were identified using ICD-10-CA procedure codes, and/or OHIP physician billing codes (Appendix). In-hospital mortality and hospital length of stay are also reported.

In objective #2, the clinical course of patients who are managed non-operatively for a first episode of diverticulitis are characterized. The outcomes of interest are readmission and emergency surgery for recurrent diverticulitis. Readmission was identified by any subsequent
urgent hospital admission for a principal diagnosis of acute colonic diverticulitis during the follow-up period, and emergency surgery was identified by urgent admission for diverticulitis with an ICD-10-CA procedure code for colectomy, colostomy, diagnostic laparoscopy or laparotomy, or operative (non-percutaneous) abscess drainage during the admission (for relevant codes, see Appendix 1). We censored the first 30 days after the index admission, believing events occurring within this interval were more likely persistent, rather than recurrent disease. Thus observation began at 30 days post-discharge for all patients. This approach is consistent with definitions of disease recurrence in prior reports\textsuperscript{187}. Follow-up continued for all patients until the occurrence of the event of interest, the occurrence of a competing event (elective colectomy, death), or end of the follow-up period (March 31, 2012).

In objective #3, we characterize the clinical outcomes and temporal trends associated with elective colectomy following initial non-operative management of diverticulitis. Elective colectomy was identified by an elective hospital admission for a principal diagnosis of acute colonic diverticulitis with an ICD-10-CA procedure code for any colectomy. Specific operative strategies used in elective surgery (laparoscopy and bowel exteriorization) were identified using ICD-10-CA intervention codes (Appendix). In-hospital mortality and hospital length of stay (LOS) were also evaluated. We censored events occurring within the first 30 days after discharge, as operations taking place within this early interval were more likely to reflect persistent index disease. Thus observation began at 30 days post-discharge for all patients. Follow-up continued for all patients until elective colectomy was performed, or until occurrence of a competing event (emergency operation for diverticulitis, all-cause mortality), or end of the study follow-up period (March 31, 2012).
2.6 Statistical Analysis

Statistical analyses were performed using SAS, version 9.3 (SAS Institute, Cary, North Carolina). Descriptive results are presented as medians (inter-quartile range, IQR) for continuous data, and as counts (percentages) for categorical data. Categorical variables were compared using the Pearson $\chi^2$ statistic and non-normal continuous variables were evaluated using Wilcoxon rank sum test or Kruskal-Wallis test. Two-tailed p-values less than 0.05 were considered statistically significant.

Cochran-Armitage was used to test for trends over time for binary outcomes; linear regression was used to test for trends for continuous outcomes. Multivariable logistic regression with generalized estimating equations (GEE) was used to adjust for patient and disease characteristics while determining the effect of time (calendar year) on treatment strategies. When analyzing large multi-site cohorts like the one used in this study, subjects are often “clustered” within healthcare sites, such that patients being treated at the same site are often more similar to one another than to patients treated at a different site. This suggests that observations within the cohort are not independent of each other. Unlike the more commonly used generalized linear models, which assumes that all observations are independent, models using generalized estimating equations has the ability to adjust for the correlated nature of the observations\textsuperscript{188}. Adjusted odds ratios with 95% confidence intervals are reported.

2.6.1 Competing risks in time-to-event analysis

Time-to-event (survival) analysis was used to estimate the risk of readmission and emergency surgery for recurrent diverticulitis at various time points following initial non-operative management. Advantages of time to event analysis include the ability to account for
variable periods of follow-up time as well as censoring, which occurs when follow-up for a patient ends before the outcome is observed (for example, a subject may not have experienced the outcome of interest before the end of the observation window). This is referred to as non-informative censoring, which assumes that any subject who is censored would have experienced the event of interest if followed for long enough. When there is only one possible type of event (e.g., all-cause mortality), censoring is non-informative.

However, simple censoring should not be used when the subject experiences another outcome that precludes the subject from experiencing the outcome of interest. In the present study for example, a patients may die from other causes unrelated to diverticular disease or undergo elective colectomy during the follow-up period, thereby entirely eliminating or greatly reducing their risk of experiencing disease recurrence and need for emergency operation. Such events that make the outcome of interest less likely or impossible to observe are referred to as competing risks. When competing events are present, the assumption of non-informative censoring is violated, and statistical analyses that use the standard product-limit method of describing the distribution of time to event are no longer appropriate\textsuperscript{189,190}, so commonly used statistical methods such as Kaplan-Meier curves, log-rank tests, and Cox proportional hazards models can no longer be used. It has been demonstrated that when competing events are present to a significant degree, the Kaplan-Meier method is biased and will overestimate the probability of the outcome\textsuperscript{189,106,107}.

The cumulative incidence approach has been developed as an alternative analytic method to explicitly account for the presence of competing events\textsuperscript{107,108}. While the product-limit estimate of probability of an event will reach 1 with an infinite follow-up time, the cumulative incidence estimate never reaches 1 because a proportion of patients will experience the
competing event. The cumulative incidence function is the cumulative probability of failure from a specific cause over time. Simply put, the cumulative incidence approach describes the probability of the outcome as actually observed in the study cohort. Unlike the commonly used Kaplan–Meier method which censors for competing events, a cumulative incidence approach explicitly accounts for the presence of competing risk events \(^{189}\).

We therefore estimated the cumulative incidences of readmission and emergency surgery, as well as of the competing events death and elective colectomy, at various time points following discharge. Patients who did not experience any event by the end of the study were censored. We performed a sensitivity analysis to assess the impact of censoring events occurring within the first 30 days following discharge. Using SAS macro %CIF, Gray’s modified log-rank test was used to compare unadjusted incidence estimates and to evaluate the equality of cumulative incidence curves between groups.

### 2.6.2 Multivariable analysis with competing events data

Standard Cox proportional hazard models do not allow for the analysis of competing events, and therefore multivariable regression was performed using a Fine and Gray competing risk model to determine the patient factors associated with increased risk of readmission and emergency surgery for diverticulitis, while accounting for the occurrence of death and elective surgery as competing events \(^{190,191}\). Fine and Gray proposed a proportional subdistribution model that models differences in the cumulative incidence of the event of interest \(^{191}\), its estimation is based on modified risk sets where subjects experiencing the competing event are retained even after their event. These individuals can be viewed as “placeholders” for the proportion of the population that cannot have the event of interest \(^{192}\). With this model, a subdistribution hazard
function is defined as the probability of the event given that an individual has survived up to time \( t \) without any event or has had the competing event prior to time \( t \). With increasing time, the risk set is comprised of an increasing proportion of individuals who have the competing event. At any given time, the subdistribution hazard is smaller than the cause-specific hazard because of the larger risk set\(^{192}\).

For our analysis, we used a SAS macro “pshreg” created by Kohl and Heinze at the Medical University of Vienna, which implements the Fine and Gray model to fit a proportional subdistribution hazards model for survival data subject to competing risks\(^{190}\). This macro first modifies the input dataset and then applies standard SAS Cox regression (proc phreg) using weights and counting-process style of specifying survival times to the modified dataset. The proportional hazards assumption was tested graphically by plotting log-negative log survival against the log of time, and by testing for the significance of covariate-time interaction terms. Adjusted sub-distribution hazard ratios with 95% confidence intervals are reported. Where proportionality assumptions are violated, time-specific hazard ratios are reported instead.
Chapter 3
Temporal Trends in the Management of Acute Diverticulitis

Preamble:

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3.1 Abstract

**Background:** There is increasing evidence to support the use of percutaneous abscess drainage, laparoscopy, and primary anastomosis in managing acute diverticulitis.

**Objective:** To evaluate how practices have evolved and determine effects on clinical outcomes.

**Design:** Population-based retrospective cohort study using administrative discharge data.

**Setting:** Ontario, Canada.

**Patients:** All patients hospitalized for a first episode of acute diverticulitis (2002-2012).
Main Outcome Measures: Temporal changes in treatment strategies and outcomes were evaluated using Cochran-Armitage test for trends. Multivariable logistic regression with generalized estimating equations was used to test for trends while adjusting for patient characteristics.

Results: There were 18,543 patients hospitalized with a first episode of diverticulitis, median age 60 years [inter-quartile range: 48-74]. From 2002 to 2012, there was an increase in the proportion of patients admitted with complicated disease (abscess, perforation): 32% to 38%, yet a smaller proportion underwent urgent operation: 28% to 16% (all p<0.001). Use of percutaneous drainage increased from 1.9% of admissions in 2002 to 3.3% in 2012 (p<0.001). After adjusting for changes in patient and disease characteristics over time, the odds of urgent operation decreased by 0.87 per annum (95% CI: 0.85-0.89). In those undergoing urgent surgery (n=3,873), use of laparoscopy increased (9% to 18%, p<0.001), while use of Hartmann’s remained unchanged (64%). During this time, in-hospital mortality decreased (2.7% to 1.9%), as did median length of stay [5 days (IQR 3-9) to 3 days (IQR 2-6)] (p<0.001).

Limitations: There is the potential for residual confounding, as clinical parameters available for risk adjustment were limited to fields existing within administrative data.

Conclusions: There has been an increase in the use of non-operative and minimally-invasive strategies in treating patients with a first episode of acute diverticulitis. However, Hartmann’s procedure remains the most frequently employed urgent operative approach. Mortality and length of stay have improved during this time.
3.2 Introduction

Diverticulitis of the colon is a common reason for both urgent and elective hospital admission, accounting for nearly one third of all colon resections and colostomies.\textsuperscript{89} It is a significant burden on healthcare resources at an estimated cost of $2.6 billion (US) per annum.\textsuperscript{31} Furthermore, rates of diverticulitis are increasing in many developed nations related to an aging population, low dietary fiber intake, and rising rates of obesity.\textsuperscript{28, 33, 44, 193, 194}

Management of acute diverticulitis has evolved over time; indications for operative intervention and the best operative approaches in the emergency setting remain unclear.\textsuperscript{52, 110} The threshold for urgent operative intervention during an acute episode of diverticulitis may be increasing as advances in diagnostic imaging, medical management, and percutaneous abscess drainage allow for non-operative approaches to managing complicated diverticulitis.\textsuperscript{57, 90, 144, 149} Additionally, operative strategies are changing when urgent surgical intervention is required. For example, several reports have demonstrated that primary anastomosis, with or without diverting ileostomy, is a safe alternative to Hartmann’s procedure for complicated and perforated diverticulitis,\textsuperscript{72, 98, 104, 105, 195} and the safety and potential benefits of laparoscopic approaches in the emergency setting are becoming established.\textsuperscript{115, 119, 120, 196-199}

Taken together, there is increasing evidence to support changes in the management of acute diverticulitis. The aim of this study was to characterize the extent to which this evidence has been translated into practice. Specifically, our objectives were to evaluate temporal changes in (1) the use of non-operative management strategies for acute colonic diverticulitis, (2) the surgical approaches used during urgent operative intervention, including the use of Hartmann’s
procedure and laparoscopic techniques, and (3) patient outcomes, including in-hospital mortality and length of hospital stay.

### 3.3 Methods

**Study Design and Setting:**

This was a population-based retrospective cohort study evaluating the management of patients with a first episode of acute colonic diverticulitis in the province of Ontario, Canada. Ontario is Canada’s most populous province with over 13 million residents, all of whom receive medically-necessary physician and hospital services paid for by the provincial government in a publically-funded healthcare system. This study was approved by the Research Ethics Board at Sunnybrook Health Sciences Centre.

**Data Sources:**

The study cohort was derived from administrative health datasets housed at the Institute of Clinical Evaluative Sciences (ICES), Toronto, Ontario, Canada. The Canadian Institute of Health Information (CIHI) Discharge Abstract Database (DAD) provides demographic information, diagnoses, procedures performed, and discharge information for all hospital admissions in the province, coded by the *International Classification of Disease, Tenth Revision-Canada (ICD-10-CA)*. The National Ambulatory Care Reporting System (NACRS) captures data for all ambulatory care visits, including emergency department (ED) visits. Procedural codes were also obtained from physician billings to the Ontario Health Insurance Plan (OHIP). The Registered Persons Database (RPDB) provided information on vital statistics. An encrypted unique patient identifier allowed data linkage across administrative databases.
Cohort:

All residents 18 years of age or older who were admitted through any emergency department in Ontario with a most responsible diagnosis of acute colonic diverticulitis from April 1, 2002 to March 31, 2012 were considered for inclusion (ICD-10-CA diagnosis codes K57.2 and K57.3, encompassing patients with diverticulitis in any location of the colon). To identify only those patients with a first episode of diverticulitis, we excluded patients who had any previous hospital admissions or ED visits for colonic diverticulitis dating back to the initiation of these administrative databases (1988 for hospital admissions, 2000 for ED visits). We also excluded patients who presented with concurrent gastrointestinal bleeding and those with a history of colorectal cancer or colectomy (for relevant codes, see Appendix).

Variable Definitions:

Primary exposure: Given the focus on trends in management strategies and outcomes over time, the primary exposure of interest was calendar year, from 2002 to 2012.

Covariates: Patient characteristics (age, sex, comorbidity burden, income quintile, and rural residency) as well as disease severity were evaluated as potential confounders. These variables were treated as covariates in multivariable regression analysis. Young age was defined in this study as age less than 50 years at the time of index presentation. Comorbidities were captured using the Deyo adaptation of the Charlson Comorbidity Index (CCI), calculated from health administrative records in the one year prior to admission. Income quintile was calculated using median neighborhood (dissemination area) household income by postal code and Canadian census data. Urban residence was defined as living within a Statistics Canada census metropolitan area or census agglomeration with an urban core of >10,000 people.
ICD-10-CA codes for uncomplicated diverticulitis (K57.3 – no perforation or abscess) or complicated diverticulitis (K57.2 – with perforation or abscess) were used to estimate disease severity.

Outcomes: A patient was deemed to have had an operative intervention if there was a concurrent ICD-10-CA procedure code for colectomy, colostomy, diagnostic laparoscopy or laparotomy, or operative (non-percutaneous) abscess drainage during the hospital admission (for relevant codes, see Appendix). The specific management strategies (percutaneous abscess drainage, laparoscopy, Hartmann’s procedure) and the time from hospital admission to operative intervention were identified using ICD-10-CA procedure codes, and/or OHIP physician billing codes (Appendix). In-hospital mortality and hospital length of stay were also reported.

Statistical Analysis:

Statistical analyses were performed using SAS, version 9.3 (SAS Institute, Cary, North Carolina). Descriptive results are presented as medians and inter-quartile range (IQR) for continuous data, and as counts and percentages for categorical data. Categorical variables were compared using the Pearson $\chi^2$ statistic and non-normal continuous variables were evaluated using Wilcoxon rank sum test or Kruskal-Wallis test. All tests were two sided and p-values less than 0.05 were considered statistically significant.

The proportion of admitted patients undergoing urgent operative intervention and specific operative strategies were calculated for each calendar year. Cochran-Armitage was used to test for trends over time for binary outcomes; linear regression was used to test for trends for continuous outcomes. Multivariable logistic regression with generalized estimating equations (GEE) was used to adjust for patient and disease characteristics while determining the effect of
time (calendar year) on treatment strategies. GEE was used to account for potential clustering of patients at hospital sites. Adjusted odds ratios with 95% confidence intervals are reported.

3.4 Results

There were 18,543 patients with a first episode of diverticulitis hospitalized in 161 different centers over 2002-2012. The median age of the cohort was 60 years [IQR 48-74 years], and 53% were female (table 1). Of this cohort, 3,873 (21%) underwent urgent operative intervention during the index hospital admission. The remaining patients were managed non-operatively, either with medical management alone or in combination with percutaneous abscess drainage (figure 1). Overall, 65% of admitted patients presented with uncomplicated (simple) diverticulitis, of which almost all (96%) were successfully managed non-operatively. The remaining 35% of admitted patients presented with complicated disease (abscess or perforation), of which half (49%) were successfully managed non-operatively.

When stratified by age, younger patients (age<50 years) were no more likely to present with complicated disease than patients age 50 years or older (34.9% vs 35.3%, p=0.62). However, older patients had a higher rate of urgent operative intervention during their index admission (22% vs 19%, p<0.001). Patients treated operatively had a greater burden of medical comorbidities and were more likely to have complicated disease (table 1).

Patients were most likely to undergo surgery on the day of hospital admission. Of the 3,873 patients who were treated operatively, 56% underwent surgery on the day of admission, 79% underwent surgery within 2 days of admission, and 89% within 5 days of admission.

Temporal trends in management strategies
The absolute numbers of diverticulitis admissions increased over time (figure 2). From 2002 to 2012, there was an increase in the proportion of patients admitted to hospital with complicated disease: from 32% in 2002 to 38% of admissions in 2012 (p<0.001). In spite of this increasing rate of complicated disease, patients were less likely to undergo operative intervention (28% in 2002 to 16% in 2012, p<0.001), a finding most pronounced among younger patients and those with complicated disease (figure 3). The use of percutaneous abscess drainage increased from 1.9% of admissions in 2002 to 3.3% in 2012 (p<0.001). In adjusted analyses, older age, greater burden of comorbidities, and complicated disease were associated with urgent operative intervention during the index admission (table 2). Overall, after adjusting for changes in patient and disease characteristics over time, the odds of urgent surgery decreased by 0.87 per annum (adjusted OR 95% CI: 0.85-0.89).

There were marked changes in operative approaches over time. Laparoscopic techniques (including diagnostic laparoscopy, laparoscopic lavage and drainage, laparoscopic resection, and laparoscopic Hartmann’s procedure) increased from 9% of surgical procedures in 2002 to 18% in 2012 (p<0.001). Younger age, lower medical comorbidity, and uncomplicated disease were associated with increased odds of laparoscopic emergency operation (table 2). After adjustment for changes in patient and disease characteristics over the decade of observation, the odds of urgent laparoscopic intervention increased by 1.14 per annum (95% CI: 1.09-1.20).

The proportion of patients managed operatively who underwent Hartmann’s procedure – performed either open or laparoscopically – did not change over time, and accounted for 64% of all urgent surgical procedures (Cochran-Armitage test of trend: p=0.61). The adjusted odds of Hartmann’s procedure were greater in older patients, males, patients with a greater comorbidity burden, and patients presenting with complicated disease (table 2). After adjusting for changes in
patient and disease characteristics, use of Hartmann’s procedure did not change over time (OR 0.98 per annum, 95% CI: 0.95-1.01).

**Changes in mortality and length of stay**

Over the interval of observation, the crude in-hospital mortality rate was 2.2%. Mortality was lower among patients managed non-operatively (0.9% vs 7.4%, p<0.001), and was lower among patients with uncomplicated disease than those with complicated disease (0.5% vs 5.3%, p<0.001). From 2002 to 2012, there was an overall decline in in-hospital mortality from 2.7% to 1.9% (p<0.001). In-hospital mortality was unchanged over time for patients with uncomplicated disease (test for trend p=0.07), whereas mortality decreased significantly for patients presenting with complicated disease (from 8.0% in 2002 to 4.3% in 2012, p<0.001). In adjusted analysis, older age, greater medical comorbidity burden, lower income, and complicated disease were associated with greater risk of mortality during the index admission (table 2). After adjusting for patient and disease characteristics, in-hospital mortality decreased with time (OR 0.90 per annum, 95% CI: 0.87-0.93).

Median length of stay (LOS) in hospital was 4 days (IQR: 3-8 days) for all admitted patients. LOS was significantly shorter for patients managed non-operatively than those managed operatively [median 4 days (IQR 2-6 days) versus 10 days (IQR: 7-17 days), p<0.001]. LOS was also significantly shorter for patients with uncomplicated disease than those with complicated disease [median 3 days (IQR 2-5 days) versus 8 days (IQR: 5-13 days), p<0.001]. Overall, length of stay in hospital decreased over time for all admitted patients, from a median of 5 days (IQR 3-9) in 2002 to 3 days (IQR 2-6) in 2012 (p<0.001). Stratified by disease complexity, LOS decreased for patients with uncomplicated disease [median 4 days (IQR 3-6 days) in 2002, decreasing to 3 days (IQR 2-4 days) by 2012, p<0.001]. LOS decreased more dramatically for
patients with complicated disease [median 9 days (IQR 6-16 days) in 2002, decreasing to 6 days (IQR 3-10 days) by 2012, p<0.001].

3.5 Discussion

We have demonstrated significant changes in the management of acute colonic diverticulitis over the past decade. The proportion of patients undergoing urgent operative intervention at index admission has decreased over time, with changes being most evident in younger patients and those presenting with complicated disease. In this cohort, almost all patients presenting with uncomplicated diverticulitis and half of patients with complicated disease were managed non-operatively. When operative intervention is required, the use of laparoscopic approaches has doubled over 2002-2012. However, Hartmann’s procedure remains the most frequently employed operative strategy, with little to no change over the past decade. In spite of the greater frequency of complicated disease, mortality rates and length of stay in hospital have decreased over time.

Overall, 21% of patients underwent operative intervention with rates as low as 16% in the last year of observation. Our findings related to increasing non-operative management are consistent with other reports, where contemporary rates of urgent operation have been reported to be as low as 12-14%. Several factors might account for these observations. For example, improved diagnostic accuracy with frequent use of cross-sectional imaging, better supportive care (including earlier and broader spectrum antimicrobials) and more aggressive approaches to image-guided percutaneous abscess drainage all might increase the probability of successful non-operative management. The more pronounced decline in operative intervention for young patients and those with complicated disease is in keeping with updated
Whether these changes might lead to higher rates of recurrence and greater resource utilization over prolonged follow-up will need to be evaluated.

A greater spectrum of surgical options with increasing evidence of efficacy has challenged traditional operative strategies for acute diverticulitis. While other investigators have reported rates of laparoscopic colectomy in the emergency setting in the range of 2.8%-7.8%, the higher observed rates of laparoscopy use in this cohort might relate to our broader definition of laparoscopic surgery to include diagnostic laparoscopy, laparoscopic lavage, resection or Hartmann’s procedure, as well as regional specific financial incentives for this approach. Use of laparoscopy for emergency cases will likely continue to increase as surgeons develop greater expertise in the elective setting and evidence accrues supporting its safety and efficacy.

Several reports have provided evidence that primary resection and anastomosis, with or without diverting ileostomy, is safe in selected patients with diverticulitis requiring urgent operation. However, adoption of this approach has been limited. Hartmann’s procedure remains the most frequently utilized operative strategy in the emergency setting, with rates remaining relatively constant over the past decade. These findings are consistent with other population-based studies where minor or no reductions in rates of colostomy have been identified, and might be attributable to two factors: 1) patients requiring operative intervention now are more likely to have complicated and severe disease, increasing the risk of a failed primary anastomosis; 2) surgeons are reluctant to perform a colorectal anastomosis in the setting of severe intra-abdominal infection. While the former might be appropriate, the latter practice might be more amenable to change over time as further evidence accrues supporting different operative strategies tailored to patient risk.
The bulk of evidence relating to the safety of primary anastomosis in this setting is derived from retrospective case series with their methodological limitations related to confounding by indication and selection bias. Few randomized trials have been published. One multicenter randomized trial comparing Hartmann’s procedure to primary anastomosis with diverting ileostomy in the setting of acute diverticulitis has been published. In this study, primary anastomosis with diversion had equivalent mortality outcomes, higher rates of stoma reversal, fewer serious complications and lower healthcare resource use than Hartmann’s procedure. However, this trial was limited by small sample size and potential biases related to surgeon influence over the randomization process. It is plausible that Hartmann’s procedure may be the safest option for high-risk patients with hemodynamic instability or significant comorbidity, providing lower-risk patients the opportunity for a less morbid intervention. However, this approach requires further study; results from ongoing trials may add new knowledge to better inform choice of operative strategies in treating acute, complicated diverticulitis.

The use of administrative health data in research provides both strengths and limitations. Such databases are uniquely able to provide a large study sample inclusive of the entire population, include all health services delivered during a hospital admission, and enable follow-up over time with minimal loss to follow-up. However, administrative datasets are not collected specifically for research purposes and therefore are limited by lack of detailed clinical information, such as the degree of physiologic derangement and the extent of intra-abdominal infection, with limited clinical variables available for risk adjustment. In this study, there was limited ability to classify severity of the disease, as the ICD-10-CA diagnosis codes for colonic diverticulitis are restricted to either K57.3 (uncomplicated diverticulitis) or K57.2 (complicated diverticulitis).
diverticulitis with abscess or perforation). This definition of complicated disease is broad and includes patients with Hinchey class II, III and IV disease. Furthermore, the definition of “perforation” can include a wide range of severity, ranging from micro- to macro-perforation, and from purulent to feculent peritonitis. We use the presence of coding for interventions such as percutaneous abscess drainage and emergency operation to help identify disease severity levels, but the lack of detailed clinical information and precise Hinchey classification remains a weakness in this study. Additionally, such data are unable to provide information regarding patient symptoms and quality of life, which represent important clinical considerations that are not captured within hospital discharge data. It is also possible that case ascertainment and identification of procedures might be compromised by inaccuracies in the ICD-10-CA diagnostic and procedural codes within the discharge database. However, prior reports have indicated good accuracy within administrative discharge data, with 84% agreement in the diagnosis of diverticulitis, and 97% agreement in intervention codes within the Discharge Abstract Database used for this study.\textsuperscript{181-183} Finally, this study was limited to an evaluation of outcomes during the index hospital admission. It is possible that increased use of non-operative management strategies during the index admission may lead to an increased risk of subsequent complicated disease requiring emergency colectomy and colostomy. However, published evidence suggests this is unlikely.\textsuperscript{34}

In summary this work has shown a significant increase in the use of non-operative and minimally-invasive management strategies in the treatment of acute diverticulitis. During this time, patient outcomes have improved. However, there is still a high rate of operative intervention and Hartmann’s procedure remains the most frequently used operative approach, which has remained unchanged over time. Optimal surgical strategy in the setting of acute
complicated diverticulitis remains controversial, further randomized trials are needed to identify the best treatment strategy and to inform practice recommendations.
Tables for Chapter 3

Table 3.6.1 - Baseline patient characteristics, comparing patients managed non-operatively to those undergoing urgent operative intervention

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>All patients (n=18,543)</th>
<th>Patients managed non-operatively (n=14,670)</th>
<th>Patients managed operatively (n=3,873)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age - Median (IQR)</td>
<td>60 (48-74)</td>
<td>59 (48-74)</td>
<td>62 (49-75)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female Sex – N (%)</td>
<td>9,783 (52.8)</td>
<td>7,799 (53.2)</td>
<td>1,984 (51.2)</td>
<td>0.032</td>
</tr>
<tr>
<td>Charlson Comorbidity Score</td>
<td>13,922 (75.1)</td>
<td>11,321 (77.2)</td>
<td>2,601 (67.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>3,171 (17.1)</td>
<td>2,374 (16.2)</td>
<td>797 (20.6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1,450 (7.8)</td>
<td>975 (6.7)</td>
<td>475 (12.3)</td>
<td></td>
</tr>
<tr>
<td>Patient income quintile - N (%)</td>
<td>3,609 (19.5)</td>
<td>2,803 (19.1)</td>
<td>806 (20.8)</td>
<td>0.133</td>
</tr>
<tr>
<td></td>
<td>3,838 (20.7)</td>
<td>3,045 (20.8)</td>
<td>793 (20.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3,659 (19.7)</td>
<td>2,891 (19.7)</td>
<td>768 (19.8)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3,648 (19.7)</td>
<td>2,906 (19.8)</td>
<td>742 (19.2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3,726 (20.1)</td>
<td>2,980 (20.3)</td>
<td>746 (19.3)</td>
<td></td>
</tr>
<tr>
<td>Location of residence - N (%)</td>
<td>16,042 (86.5)</td>
<td>12,731 (86.8)</td>
<td>3,311 (85.5)</td>
<td>0.037</td>
</tr>
<tr>
<td></td>
<td>2,493 (13.4)</td>
<td>1,933 (13.2)</td>
<td>560 (14.5)</td>
<td></td>
</tr>
<tr>
<td>Disease severity- N (%)</td>
<td>12,041 (64.8)</td>
<td>11,476 (78.2)</td>
<td>538 (13.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>6,529 (35.2)</td>
<td>3,194 (21.8)</td>
<td>3,335 (86.1)</td>
<td></td>
</tr>
</tbody>
</table>
Table 3.6.2 - Patient characteristics associated with: urgent operative intervention, in-hospital mortality, use of laparoscopy at urgent operation, and use of Hartmann’s procedure at urgent operation

| Patient Characteristic | All patients (n=18,543) | | | Patients managed operatively (n=3,873) | | |
|------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|
|                        | Adjusted OR of         | Adjusted OR of         | Adjusted OR of         | Adjusted OR of         | Adjusted OR of         |
|                        | urgent operation       | death during           | Laparoscopic Procedure | Hartmann’s Procedure   |
|                        | during admission (95% CI) | admission (95% CI)     | (95% CI)               | (95% CI)               |
| Age b                  | 1.02 (1.00-1.03)        | 1.59 (1.51-1.68)       | 0.84 (0.80-0.87)       | 1.09 (1.06-1.12)       |
| Female Sex             | 1.06 (0.97-1.16)        | 1.23 (0.92-1.64)       | 1.06 (0.86-1.31)       | 0.84 (0.72-0.97)       |
| Charlson Comorbidity Index c | 1.17 (1.13-1.22) | 1.48 (1.41-1.55) | 0.87 (0.76-1.00) | 1.12 (1.04-1.20) |
| Patient income quintile: |                         |                        |                        |                        |
| First (lowest) quintile (ref) | -                      | -                      | -                      | -                      |
| Second quintile        | 0.88 (0.76-1.02)        | 0.92 (0.70-1.21)       | 0.86 (0.60-1.22)       | 0.98 (0.79-1.20)       |
| Third quintile         | 0.95 (0.83-1.09)        | 0.71 (0.51-0.99)       | 0.95 (0.65-1.40)       | 0.92 (0.74-1.14)       |
| Fourth quintile        | 0.85 (0.74-0.97)        | 0.67 (0.52-0.86)       | 0.85 (0.59-1.24)       | 1.01 (0.81-1.26)       |
| Fifth (highest) quintile | 0.87 (0.77-0.99)  | 0.65 (0.49-0.86)       | 0.89 (0.64-1.23)       | 1.10 (0.88-1.35)       |
| Rural Residency        | 1.07 (0.91-1.25)        | 0.79 (0.54-1.17)       | 1.05 (0.70-1.59)       | 1.21 (0.95-1.53)       |
| Complicated diverticulitis | 24.38 (20.43-29.10)   | 12.39 (9.35-16.40)     | 0.18 (0.13-0.24)       | 5.68 (4.67-6.92)       |
| Calendar Year d        | 0.87 (0.85-0.89)        | 0.90 (0.87-0.93)       | 1.14 (1.09-1.20)       | 0.98 (0.95-1.01)       |

a Multivariable logistic regression with generalized estimating equations (GEE)

b Per 5 year increase
c Per 1 point increase
d Per 1 year increase
3.6 Figures for Chapter 3

Figure 3.7.1 – Outcomes at index admission

First admission for diverticulitis  
N=18,543

Urgent operative management  
N=3,873 (20.9%)

Ileostomy/Colostomy  
N=2,689 (69.4%)

No ostomy  
N=1,184 (30.6%)

Medical management  
N=14,210 (96.9%)

Non-operative management  
N=14,670 (79.1%)

Death during admission  
N=125 (0.9%)

Percutaneous abscess drain  
N=460 (3.1%)

Successful non-operative management  
N=14,545 (78.4%)
Figure 3.7.2 - Number of diverticulitis admissions by year

- Fiscal Year
- # of Diverticulitis Admissions
- Non-operative management
- Operative Management
Figure 3.7.3 - Proportion of patients undergoing urgent operation at index admission over 2002-2012, by age group (age <50 / age ≥ 50) and disease severity (complicated/ uncomplicated)
Chapter 4

Risk of Readmission and Emergency Surgery Following Non-Operative Management of Colonic Diverticulitis

Preamble

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4.1 Abstract

Objective: To characterize the clinical course of patients with diverticulitis following non-operative management and determine factors associated with readmission and subsequent emergency surgery.

Background: Clinical course of this disease remains poorly understood; indications for elective colectomy are unclear.
Methods: This was a retrospective cohort study of patients managed non-operatively after a first episode of diverticulitis in Ontario, Canada (2002-2012). Time-to-event analysis and Fine and Gray multivariable regression were used to characterize the risks of readmission and emergency surgery for diverticulitis, accounting for death and elective colectomy as competing events.

Results: 14,124 patients were followed for a median of 3.9 years (maximum 10, IQR 1.7-6.4). Five-year cumulative incidence was 9.0% for readmission, 1.9% for emergency surgery, and 14.1% for all-cause mortality. Patients age <50 years had higher incidence of readmission than patients age ≥50 (10.5% vs 8.4%, p<0.001) but not emergency surgery (1.8% vs 2.0%, p=0.52). Patients with complicated disease (abscess, perforation) were at increased risk of readmission than those with uncomplicated disease (12.0% vs 8.2%, p<0.001), as well as increased risk of emergency surgery (4.3% vs 1.4%, p<0.001). In multivariable regression, complicated disease and number of prior admissions were associated with increased risk of emergency surgery, yet age <50 years was not. Risks associated with complicated disease were non-proportional over time, being highest immediately following discharge and decreasing thereafter.

Conclusions: Absolute risks of readmission and emergency surgery are low following non-operative management of diverticulitis, providing evidence for the practice of deferring colectomy for patients without persistent symptoms or multiple recurrences.

4.2 Introduction

Patients with colonic diverticulitis are often successfully managed non-operatively during the acute episode, but remain at lifetime risk of disease recurrence and complicated recurrence requiring emergency surgery. This unpredictable clinical course has led to the practice of performing elective prophylactic colectomy for patients deemed to be at high-risk for subsequent
disease events. Traditionally, this strategy has been advocated for patients who are less than 50 years of age at first presentation, patients who present with complicated disease including perforation, fistula, and abscess, and those who have had recurrent disease\textsuperscript{53, 131, 201}.

However, these recommendations have been made based upon limited supporting data consisting mostly of small cohort studies with limited follow-up; few prospective or population-based studies exist\textsuperscript{87, 126, 128, 129}. Furthermore, existing studies have not explicitly accounted for the presence of competing events during follow-up, such as elective colectomy and death from other causes. If the risk of all-cause mortality is greater than the risk of recurrent disease, it might not be necessary to proceed with prophylactic colectomy. Without a clear understanding of the clinical course of the disease and consideration of competing risks, the indications for elective surgery remain uncertain.

The objective of this study was to characterize the clinical course of patients with diverticulitis following initial non-operative management and to provide accurate estimates of the risk of readmission and emergency surgery while explicitly accounting for the competing events of death and elective colectomy. We use an analytic approach to overcome the limitation of traditional Kaplan-Meier time to event analysis, which over-estimates the probability of an event when competing risks are present\textsuperscript{189}. Additionally, we sought to determine the patient characteristics associated with increased risk of subsequent disease events, with particular focus on age, disease severity, and multiple readmissions.

4.3 Methods

Study Design:
We used a population-based retrospective cohort design to evaluate the clinical course of patients who have an episode of diverticulitis and are successfully managed non-operatively (i.e., discharged without colectomy). This study was approved by the Research Ethics Board at Sunnybrook Health Sciences Centre.

**Data Sources:**

This study used population-based administrative health databases from the province of Ontario, Canada. The Canadian Institute of Health Information (CIHI) Discharge Abstract Database (DAD) was used to identify the study cohort. The DAD provides demographic, diagnostic, procedural, and discharge information for all hospital admissions in the province, coded by the *International Classification of Disease, Tenth Revision-Canada (ICD-10-CA).* Vital statistics were obtained from the Registered Persons Database (RPDB), an administrative database of all residents of Ontario who are alive and eligible for coverage under the publically-funded Ontario Health Insurance Plan (OHIP). An encrypted unique patient identifier allowed for deterministic linkage across datasets. All administrative databases were maintained and analyzed at the Institute of Clinical Evaluative Sciences (ICES), Toronto, Canada.

**Study Cohort:**

All Ontario residents 18 years of age or older who were admitted through any Emergency Department with a most responsible diagnosis of acute colonic diverticulitis from April 1, 2002 to March 31, 2012 were considered for study inclusion (identified by the *ICD-10-CA* diagnosis codes K57.2 and K57.3 in the DAD). To limit the cohort to patients with a first episode of diverticulitis, patients who had any previous hospital admissions or emergency department (ED) visits for colonic diverticulitis were excluded, dating back to the inception of these
administrative databases (1988 for hospital admissions, 2000 for ED visits). Patients with concurrent gastrointestinal bleeding, or any history of colorectal cancer or colectomy were also excluded (for relevant codes, please see table - supplemental digital content). Patients who were discharged from hospital without operation, and who had at least 30 days of follow-up, comprised the final study cohort.

**Outcome and follow-up:**

The outcomes of interest in this study were readmission and emergency surgery for recurrent diverticulitis. Readmission was identified by any subsequent urgent hospital admission for a principal diagnosis of acute colonic diverticulitis during the follow-up period, and emergency surgery was identified by urgent admission for diverticulitis with an ICD-10-CA procedure code for colectomy, colostomy, diagnostic laparoscopy or laparotomy, or operative (non-percutaneous) abscess drainage during the admission (for relevant codes, please see table-supplemental digital content). We censored the first 30 days after the index admission, believing events occurring within this interval were more likely persistent, rather than recurrent disease. Thus observation began at 30 days post-discharge for all patients. This approach is consistent with definitions of disease recurrence in prior reports. Follow-up continued for all patients until the occurrence of the event of interest, the occurrence of a competing event (elective colectomy, death), or end of the follow-up period (March 31, 2012).

**Patient Covariates:**

We sought to evaluate the association of age, disease severity, and number of diverticulitis admissions on the risk of experiencing subsequent disease events. Young age at first presentation was defined as age <50 years at index admission. Disease severity was
classified as uncomplicated index disease (*ICD-10-CA* diagnosis code K57.3 - diverticulitis of the large intestine without perforation or abscess), complicated disease without percutaneous abscess drainage (*ICD-10-CA* diagnosis code K57.2 - diverticulitis of the large intestine with perforation or abscess), or complicated disease with percutaneous abscess drainage (*ICD-10-CA* diagnosis code K57.2 with procedure code for percutaneous abscess drainage). The number of prior admissions was calculated as a sum of the total number of urgent hospital admissions for diverticulitis at the time just prior to urgent or elective surgery or, in those never undergoing surgical treatment, up until the time of death or end of study follow-up. The number of prior admissions was treated as a repeated events variable using a counting process model.

Baseline patient characteristics including sex, medical comorbidity burden, income quintile, rural residency, and calendar year of index admission were considered potential confounders and were therefore included in multivariable regression analysis. The Deyo adaptation of the Charlson Comorbidity Index (CCI)\textsuperscript{184} was used to represent patient medical comorbidity, calculated from hospital admission records in the one year prior to index admission. Income quintile at the time of index admission was calculated using median neighborhood household income by postal code and Canadian census data\textsuperscript{185}. Residency was classified as urban or rural based on postal code, with urban residency being defined as residing within a Census Metropolitan Area or Census Agglomeration with an urban core > 10,000 people (Statistics Canada)\textsuperscript{186}.

**Statistical Analysis:**

Statistical analyses were performed using SAS, version 9.3 (SAS Institute, Cary, North Carolina). Descriptive results are presented as medians (inter-quartile range, IQR) for continuous data, and as counts (percentages) for categorical data. Categorical variables were compared using
the Pearson χ² statistic and non-normal continuous variables were evaluated using Wilcoxon rank sum test or Kruskal-Wallis test. Two-tailed p-values less than 0.05 were considered statistically significant.

Time to event analysis was performed and cumulative incidences of readmission and emergency surgery, as well as of the competing events death and elective colectomy, were estimated at various time points following discharge. Unlike the commonly used Kaplan–Meier method which censors for competing events, a cumulative incidence approach explicitly accounts for the presence of competing risks. Patients who did not experience any event by the end of the study were censored. We also performed a sensitivity analysis to assess the impact of censoring events occurring within the first 30 days following discharge.

To determine patient factors associated with readmission and emergency surgery, Gray’s modified log-rank test was used to compare unadjusted incidence estimates and to evaluate the equality of cumulative incidence curves. Multivariable regression was performed using a Fine and Gray competing risk model to determine the patient factors associated with increased risk of readmission and emergency surgery for diverticulitis, while accounting for the occurrence of death and elective surgery as competing events. The proportional hazards assumption was tested graphically by plotting log-negative log survival against the log of time, and by testing for the significance of covariate-time interaction terms. Adjusted sub-distribution hazard ratios with 95% confidence intervals are reported. Where proportionality assumptions are violated, time-specific hazard ratios are reported instead.
4.4 Results

There were 18,543 patients admitted with a first episode of acute colonic diverticulitis over 2002-2012, of which 14,545 (78.4%) were discharged alive without operative intervention. The characteristics, management strategies, and outcomes of patients undergoing urgent operative intervention during the index admission have been reported separately (see Chapter 3). A further 197 patients were excluded for undergoing colectomy within 30 days of discharge and 224 were excluded for having less than 30 days of follow-up. This left 14,124 patients (76.2%) who remained at risk for subsequent recurrence and emergency surgery who comprised the final study cohort. Baseline characteristics for the study cohort are presented in table 1. The median follow-up time was 3.9 years (minimum 30 days, maximum 10 years, IQR: 1.7-6.4 years).

Overall outcomes of the study cohort are presented in figure 1. Of the 14,124 patients in the cohort, 1,143 (8.1%) had at least one subsequent urgent readmission for diverticulitis and 252 (1.8%) subsequently underwent urgent surgery during the follow-up period (22% of those readmitted). Characteristics of patients who experienced readmission and those who underwent urgent operation during follow-up are presented in table 1. A substantial number of patients experienced competing events during the follow-up period: 1,342 patients (9.5%) underwent elective colectomy, and 1,701 (12.0%) patients died during follow-up before experiencing any further diverticulitis-related events.

The cumulative incidences of urgent readmission and emergency operation following discharge are shown in figure 2. For perspective on the magnitude of the competing events, the cumulative incidences of all-cause mortality and elective colectomy are also presented in figure 2. Overall, patients were more likely to experience death or elective surgery than any disease-related events.
related event. For example, at five years post discharge, the cumulative incidence for urgent readmission was 9.0% and 1.9% for emergency surgery, yet the cumulative incidence of all-cause mortality was 14.1%. The risk of mortality was dependent on age: for patients age <50 years the 5-year incidence of mortality was only 1.0%, while for older patients the incidence was 19.5%.

Readmission for recurrent diverticulitis:

Of the 1,143 patients who experienced at least one readmission during follow-up, the majority (55%) experienced a readmission within the first year following discharge. Among patients being readmitted, the median time from discharge to first readmission was 258 days (IQR: 66-855 days). Of these 1,143 patients, 954 (83.5%) had just one subsequent urgent readmission during follow-up, while 189 (16.5%) had 2 or more urgent readmissions during the follow-up period. The over-all crude in-hospital mortality at urgent readmission was 1.6%.

Cumulative incidences of urgent readmission at various time points following discharge are presented in figure 3, stratified by age group and disease severity. After 5 years of follow-up, patients age < 50 years were 1.25 times more likely to experience readmission than older patients (10.5% vs 8.4%, p<0.001). Patients with complicated diverticulitis were 1.5 times more likely to experience readmission than patients with uncomplicated index disease (12.0% vs 8.2%p<0.001). Patients with complicated disease requiring percutaneous abscess drainage at index admission were at greatest risk of readmission (figure 3).

A Fine and Gray multivariable competing risk regression analysis was performed to determine the factors associated with increased risk of readmission. After adjusting for patient sex, medical comorbidity burden, income, rural residency, and calendar year of index admission,
age < 50 years and complicated disease at index admission were associated with increased risk of readmission (table 2). As the proportional hazards assumption was violated for the disease severity stratum we included severity-time interaction terms in the model and reported time-specific hazard ratios. The changing time-specific hazard ratios by disease severity strata are presented in figure 4(a), demonstrating the increased risk associated with having complicated disease is highest immediately following discharge but decreases over time. The risk was highest for patients with complicated disease requiring percutaneous abscess drainage.

**Emergency surgery for recurrent diverticulitis:**

A total of 252 patients underwent emergency surgery for diverticulitis over the follow-up interval. The median time to urgent operation for patients experiencing the event was 132 days (IQR: 48-554 days), with 70% of urgent operations occurring in the first year after discharge. Of the patients who undergo emergency operation, 61% received an ileostomy or colostomy and in-hospital mortality was 5.2%.

Cumulative incidences of emergency surgery for diverticulitis at various time points following discharge are presented in figure 5, stratified by age group and disease severity. In unadjusted analyses, at five years post-discharge, patients age < 50 years of age at index admission were no more likely to have undergone emergency surgery than those > 50 years (1.8% vs 2.0%, p=0.52). Stratified by disease severity, patients with complicated diverticulitis at index admission were 3.1 times more likely to have undergone emergency surgery by 5 years post-discharge (4.3% vs 1.4%, p<0.001).

A Fine and Gray multivariable competing risk regression was performed to determine the patient factors associated with an increased risk of emergency surgery during follow-up. After
adjusting for other factors, age<50 years was not associated with increased risk of subsequent emergency surgery. Compared to patients with uncomplicated diverticulitis at the index admission, those with complicated disease were at increased risk of requiring emergency surgery during follow-up, particularly patients who required percutaneous abscess drainage (table 2). As the proportional hazards assumption was violated, severity-time interaction terms were included in the regression model and time-specific hazard ratios are reported. The change in hazard ratios over time is shown in figure 4(b). As with readmission, the increased risk of emergency surgery for patients with complicated index disease is highest immediately following discharge and subsequently decreases over time.

**Sensitivity analysis:**

To determine the effects of censoring patients with events in the first 30 days after discharge, we performed a sensitivity analysis while including events occurring within the first 30 days. The 5-year cumulative incidence of readmission was 12.1% (vs.9.0% when excluding events within 30 days), and the 5-year cumulative incidence for emergency operation was 2.9% (vs. 1.9% when excluding events within 30 days). Including these events in the adjusted analyses did not alter the findings.

**4.5 Discussion**

In this population-based retrospective cohort analysis, we characterized the clinical course of patients with diverticulitis initially treated without surgery. We have demonstrated that the long-term risks of readmission and emergency surgery are low. At 5 years post discharge, the cumulative incidence of readmission was 9.0%, and the cumulative incidence of emergency surgery was 1.9%. Furthermore, for patients age 50 years or older, the incidence of death was
nearly 10 times greater than the incidence of emergency surgery at 5 years of follow-up (19.5% vs 2.0%). Age <50 years, complicated index disease, and greater number of prior episodes infer a greater relative risk of subsequent disease events. However, the absolute risks of readmission and emergency surgery remain low even for patients with these known risk factors, and may not justify the risks associated with elective prophylactic colectomy.

Prior reports evaluating the risk of readmission or emergency surgery following non-operative management of diverticulitis have consisted predominantly of single or multi-institution cohort studies with limited follow-up. In the few studies using population-based analysis or large administrative datasets, readmission rates have ranged from 13-19% \(^{87, 129, 170}\). The probability of subsequent emergency surgery from large retrospective cohort studies and population-based studies have ranged from 1.4% to 8.3% \(^{88, 126-129}\). The lower incidence of readmission and emergency surgery in the current study may be attributable to more contemporary management strategies, the exclusion of early events within 30 days of discharge (admissions more likely to reflect persistent, rather than recurrent disease), as well as the explicit accounting of competing risks, as opposed to the traditional Kaplan-Meier method, which is known to overestimate the event of interest when competing events occur at a significant rate \(^{189}\).

Young age at first presentation has traditionally been considered a poor prognostic factor \(^{62, 129, 134, 202-204}\), with earlier guidelines recommending routine elective colectomy for patients less than 50 years of age at first presentation \(^{131}\). However, more recent data suggests that younger patients may not have more virulent disease \(^{135, 137, 138}\), which has been incorporated into contemporary practice guidelines \(^{52, 53}\). Two meta-analyses have compared the clinical course for patients younger and older than age 50 \(^{141, 142}\), both found young age to be associated with increased risk of readmission (pooled relative risk: 1.7). Van de Wall et al also found that young
patients were at increased risk of subsequent emergency operation, with a pooled RR of 1.46 for young patients (95% CI: 1.29-1.66)\textsuperscript{141}. However, these findings were based on data from only 4 cohort studies and were sensitive to the exclusion of the dominant population-based study. Our findings shed further light on the relationship between age and subsequent disease events. While our study confirmed that age less than 50 years at index presentation was associated with a higher risk of readmission, we did not observe a higher risk of emergency surgery. Furthermore, the estimated incidence of readmission was 10.5% at 5 years for young patients, and the risk of emergency surgery is even lower at 1.8%. These data suggest that the majority of young patients who have had an episode of diverticulitis treated non-operatively will not experience further disease events, and will not benefit from elective colectomy.

Complicated diverticulitis accounts for up to 20-30\% of cases of diverticulitis\textsuperscript{31}, yet little is known about the clinical course of patients with complicated disease managed without elective operation. Percutaneous abscess drainage has traditionally been used as a bridge towards colectomy, allowing the patient to have an elective single stage procedure with reduced risk of morbidity and stoma creation\textsuperscript{53,147}. In practice, the majority of patients who require percutaneous drainage of abscess for diverticulitis do undergo elective colectomy following discharge\textsuperscript{143}. Few studies have evaluated the clinical course of such patients without further intervention, and those that have are limited by small sample size and high loss to follow-up\textsuperscript{57, 64, 86, 124, 143, 148-152}. However, there is increasing evidence to suggest that percutaneous drainage alone may be sufficient treatment for complicated diverticulitis\textsuperscript{143, 148}.

In the current study, complicated index disease, especially disease requiring percutaneous abscess drainage, was associated with increased risk of readmission and subsequent emergency surgery. The risk varies over time, being highest immediately following discharge and
decreasing thereafter. However, the absolute risk of subsequent disease events in this study was much lower than the recurrence rates of 24%-53% observed in prior reports\textsuperscript{15, 57, 127, 143, 148}. In the current study, 85% of patients with complicated index disease successfully managed non-operatively did not require readmission, and greater than 90% did not require emergency surgery. These data suggest that non-operative management strategies may be appropriate even for patients with complicated diverticulitis. Further research is warranted to determine characteristics that predict increased risk of recurrence and urgent operation following successful abscess drainage, reports to date suggest factors such as abscess location, abscess size, and patient comorbidity may be associated with increased risk\textsuperscript{86, 143, 152}, elective colectomy may be best reserved for patients who have complicated disease with high-risk characteristics.

This study has many strengths, including a population-based approach with large sample size and extended duration of follow-up. Further, we accurately take into consideration the competing risks of death and elective colectomy. However, some limitations warrant discussion. As with all observational studies, the role of selection bias and confounding by indication cannot be excluded. Results may be biased if patients who are at the highest risk for readmission and emergency surgery are preferentially selected to undergo elective colectomy. However, only 9.5% of the cohort underwent elective surgery during follow-up. Even if half of these patients would have experienced subsequent disease events without elective surgery the estimated overall incidences of readmission and emergency operation would only approach 15% and 7% respectively, making it unlikely that selection bias has significantly changed the conclusions drawn from this study.

Administrative datasets have the unique advantage of providing information for entire populations with minimal loss to follow-up, but its use also confers limitations that must be taken
into consideration in interpreting our results. As the data are not collected specifically for research purposes, administrative health data lack detailed clinical information, such as severity of disease and degree of physiological derangement, thereby limiting the variables available for risk adjustment and allowing for the possibility of residual confounding. Furthermore, patient-reported factors such as ongoing symptomology and reduced quality of life are not available from administrative records, which represent important clinical outcomes and frequent indications for operative intervention. Administrative data may also be limited by misclassification and potential inaccuracies in the diagnosis and intervention codes. For example, subsequent complications such as gastrointestinal bleeding, fistula, or bowel obstruction that occur during the follow-up period but are not specified with a primary diagnosis code for diverticulitis would not be captured in the analysis, which might lead to an underestimation of complication rates during follow-up. Assumptions must be made in the interpretation of administrative records which may be inaccurate. For example, we have assumed that any operation that takes place during an urgent readmission for diverticulitis represents an emergency operation in response to complicated or perforated recurrent disease. In reality, a proportion of such operations may actually have been elective or semi-urgent in nature, in response to patient or surgeon preference to operate on patients who are traditionally thought to be at high risk for subsequent events. However, such a misclassification error would actually lead to a conservative overestimate of the risk of subsequent emergency operation for our cohort, lending further support to our conclusions. Furthermore, prior reports have demonstrated a high degree of accuracy in administrative discharge data when compared to chart abstraction, with 84% agreement in the diagnosis of diverticulitis, and 97% agreement in intervention codes 181-183.
Finally, we included only hospital readmissions to define recurrent events, and excluded diagnoses of diverticulitis among patients evaluated in the outpatient setting (emergency department or ambulatory clinics). This approach is consistent with the methodology used in other studies derived from population-level or administrative health data, but leads to an underestimate of the true disease recurrence rate, as many patients might be successfully managed in the outpatient setting. We elected to exclude outpatient records due to the challenges in rendering a diagnosis of diverticulitis in the ambulatory setting, as many patients with a documented history of diverticular disease might receive a diagnosis and empiric antibiotics for symptoms without confirmatory investigations. The accuracy of outpatient diagnosis codes have been questioned by those using administrative data for research, and reports have demonstrated lower accuracy for diagnostic codes obtained from outpatient data compared to inpatient data. For example, in one validation study, the positive predictive value of diverticulitis diagnosis codes was 97% in inpatient administrative records, compared to only 76% in outpatient records. Therefore, our study results should not be interpreted as estimating the overall risk of disease recurrence or recurrent symptoms, as our objective was only to estimate the risk of experiencing clinically significant recurrence that requires readmission or urgent operation - the true risk of disease recurrence would be higher than the 8% readmission rate demonstrated in the current study.

In summary, we demonstrate that patients who have had an episode of diverticulitis managed non-operatively remain at low risk of hospital readmission and very low risk of requiring emergency operation. This clinical trajectory remains true even for patients with traditional risk factors such as young age and complicated index disease. Taken together, our results suggest that elective prophylactic colectomy may be unwarranted for the majority of
patients who have had an episode of diverticulitis managed non-operatively, and may not have any role in preventing emergency surgery. This lends further support for the practice of deferring elective colectomy for patients without persistent chronic symptoms or multiple frequent recurrences.
### 4.6 Tables for Chapter 4

**Table 4.6.1** - Baseline patient characteristics for (a) all patients, (b) patients who experience one or more urgent readmissions, and (c) patients undergoing emergency operation during follow-up

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>All patients (n=14,124)</th>
<th>Patients experiencing urgent readmission (n=1,143)</th>
<th>Patients undergoing emergency surgery (n=252)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>Age - Median (IQR)</td>
<td>59 (48-74)</td>
<td>56 (46-70)</td>
<td>59 (49-70)</td>
</tr>
<tr>
<td>Female</td>
<td>7,466 (52.9)</td>
<td>623 (54.5)</td>
<td>144 (57.1)</td>
</tr>
<tr>
<td>Charlson Comorbidity Score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>11,012 (78.0)</td>
<td>925 (80.9)</td>
<td>196 (77.8)</td>
</tr>
<tr>
<td>1</td>
<td>1,665 (11.8)</td>
<td>135 (11.8)</td>
<td>39 (15.5)</td>
</tr>
<tr>
<td>2+</td>
<td>1,447 (10.2)</td>
<td>83 (7.3)</td>
<td>17 (6.8)</td>
</tr>
<tr>
<td>Patient income quintile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lowest quintile</td>
<td>2,673 (18.9)</td>
<td>247 (21.6)</td>
<td>58 (23.0)</td>
</tr>
<tr>
<td>Second quintile</td>
<td>2,927 (20.7)</td>
<td>253 (22.1)</td>
<td>61 (24.2)</td>
</tr>
<tr>
<td>Third quintile</td>
<td>2,785 (19.7)</td>
<td>219 (19.2)</td>
<td>57 (22.6)</td>
</tr>
<tr>
<td>Fourth quintile</td>
<td>2,803 (19.9)</td>
<td>218 (19.1)</td>
<td>41 (16.3)</td>
</tr>
<tr>
<td>Highest quintile</td>
<td>2,892 (20.5)</td>
<td>202 (17.7)</td>
<td>34 (13.5)</td>
</tr>
<tr>
<td>Location of residence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>12,268 (86.9)</td>
<td>1,018 (89.1)</td>
<td>228 (90.5)</td>
</tr>
<tr>
<td>Rural</td>
<td>1,850 (13.1)</td>
<td>125 (10.9)</td>
<td>24 (9.5)</td>
</tr>
<tr>
<td>Disease severity at index admission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncomplicated</td>
<td>11,172 (79.1)</td>
<td>831 (72.7)</td>
<td>138 (54.8)</td>
</tr>
<tr>
<td>Complicated, no abscess drain</td>
<td>2,543 (18.0)</td>
<td>258 (22.6)</td>
<td>90 (35.7)</td>
</tr>
<tr>
<td>Complicated, with abscess drain</td>
<td>409 (2.9)</td>
<td>54 (4.7)</td>
<td>24 (9.5)</td>
</tr>
<tr>
<td>Number of admissions for diverticulitis *</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (index admission only)</td>
<td>12,981 (91.9)</td>
<td>-</td>
<td>194 (77.0)</td>
</tr>
<tr>
<td>2</td>
<td>954 (6.8)</td>
<td>954 (83.5)</td>
<td>41 (16.3)</td>
</tr>
<tr>
<td>3+</td>
<td>189 (1.3)</td>
<td>189 (16.5)</td>
<td>17 (6.8)</td>
</tr>
</tbody>
</table>

*Represents total number of urgent hospital admissions for diverticulitis. For patients who undergo emergency operation, this represents the number of urgent hospital admissions managed non-operatively before undergoing emergency operation.
Table 4.6.2 - Factors associated with increased risk of readmission and emergency surgery *

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Adjusted HR for Readmission (95% CI)</th>
<th>Adjusted HR for Emergency Surgery (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young Age (&lt;50 years)</td>
<td>1.24 (1.09-1.41)</td>
<td>0.83 (0.62-1.11)</td>
</tr>
<tr>
<td>Female Sex</td>
<td>1.14 (1.02-1.29)</td>
<td>1.26 (0.97-1.63)</td>
</tr>
<tr>
<td>Charlson Comorbidity Index (per 1 point)</td>
<td>0.91 (0.85-0.97)</td>
<td>0.89 (0.79-1.01)</td>
</tr>
<tr>
<td>Income Quintile:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lowest quintile (ref)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2\textsuperscript{nd} quintile</td>
<td>0.94 (0.79-1.12)</td>
<td>0.98 (0.68-1.41)</td>
</tr>
<tr>
<td>3\textsuperscript{rd} quintile</td>
<td>0.85 (0.71-1.01)</td>
<td>1.04 (0.71-1.50)</td>
</tr>
<tr>
<td>4\textsuperscript{th} quintile</td>
<td>0.82 (0.68-0.98)</td>
<td>0.67 (0.45-1.01)</td>
</tr>
<tr>
<td>Highest quintile</td>
<td>0.73 (0.61-0.88)</td>
<td>0.56 (0.36-0.85)</td>
</tr>
<tr>
<td>Rural residency</td>
<td>0.81 (0.67-0.98)</td>
<td>0.71 (0.47-1.09)</td>
</tr>
<tr>
<td>Number of prior admissions (per each additional)</td>
<td>n/a</td>
<td>2.41 (2.04-2.85)</td>
</tr>
<tr>
<td>Index disease severity:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncomplicated disease (ref)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complicated, no abscess drainage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 30 days post discharge</td>
<td>2.38 (1.93-2.95)</td>
<td>4.03 (2.73-5.93)</td>
</tr>
<tr>
<td>At 1 year post discharge</td>
<td>1.95 (1.66-2.29)</td>
<td>3.38 (2.51-4.54)</td>
</tr>
<tr>
<td>At 3 years post discharge</td>
<td>1.59 (1.38-1.84)</td>
<td>2.83 (2.10-3.81)</td>
</tr>
<tr>
<td>At 5 years post discharge</td>
<td>1.42 (1.21-1.65)</td>
<td>2.55 (1.81-3.60)</td>
</tr>
<tr>
<td>Complicated, with abscess drainage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 30 days post discharge</td>
<td>4.01 (2.72-5.90)</td>
<td>8.47 (4.55-15.77)</td>
</tr>
<tr>
<td>At 1 year post discharge</td>
<td>2.78 (2.08-3.73)</td>
<td>5.86 (3.74-9.20)</td>
</tr>
<tr>
<td>At 3 years post discharge</td>
<td>1.93 (1.42-2.63)</td>
<td>4.06 (2.21-7.44)</td>
</tr>
<tr>
<td>At 5 years post discharge</td>
<td>1.56 (1.08-2.26)</td>
<td>3.27 (1.48-7.21)</td>
</tr>
<tr>
<td>Calendar Year of Index Admission</td>
<td>0.99 (0.97-1.01)</td>
<td>0.98 (0.94-1.03)</td>
</tr>
</tbody>
</table>

*Fine and Gray competing risk multivariable regression model
4.7 Figures for Chapter 4

Figure 4.7.1 - Follow-up of non-operative treatment cohort after discharge
Figure 4.7.2. - Cumulative incidence of urgent readmission, emergency surgery, and competing events (death, elective colectomy)
Figure 4.7.3 - Cumulative incidence of readmission (a) by age stratum, (b) by severity of index disease
Figure 4.7.4 - Time-varying hazard ratios for (a) readmission and (b) emergency surgery, comparing complicated disease (without abscess drain, with abscess drain) to uncomplicated disease.
Figure 4.7.5 - Cumulative incidence of emergency surgery (a) by age stratum, (b) by severity of index disease
5.1 Abstract

Background: Indications for interval elective colectomy following diverticulitis are unclear; evidence lends increasing support for non-operative management.

Objective: To evaluate temporal trends in the use of elective colectomy following an episode of diverticulitis.

Design: Population-based retrospective cohort study using administrative discharge data.

Setting: Ontario, Canada.

Patients: Patients who have had an episode of diverticulitis managed non-operatively and were eligible for elective colectomy over 2002-2012.

Main Outcome Measures: Changes in the proportion of patients who undergo elective colectomy following an episode of diverticulitis treated non-operatively were evaluated. Cochran-Armitage was used to test for trends and adjusted analyses was performed using multivariable logistic regression with generalized estimating equations.

Results: A total of 14,124 patients were admitted with an episode of diverticulitis and treated non-operatively, making them eligible for interval elective colectomy. Median follow-up was 3.9
years [maximum 10, interquartile range (IQR) 1.7-6.4]. Overall, 1,342 (9.5%) patients underwent elective colectomy, of which 33% were performed laparoscopically and 7.5% had an associated stoma. In-hospital mortality was 0.2%. The majority (76%) of elective operations were performed within 1 year of discharge (median 160 days, IQR 88-346). The proportion of patients undergoing elective colectomy within 1 year of discharge declined from 9.6% of patients in 2002 to 3.9% by 2011 (p<0.001). The decline was most pronounced in patients <50 years of age (17% to 5%), and those with complicated disease (28% to 8%) (all p<0.001). In multivariable regression, younger age, lower medical comorbidity, complicated disease, and early readmission were associated with elective colectomy. After adjusting for changes in patient characteristics over time, the odds of elective surgery decreased by 0.93 per annum (adjusted OR 95% CI: 0.90-0.95).

Limitations: Administrative health databases contain limited clinical detail; rationale for elective surgery was unavailable.

Conclusions: Consistent with evolving practice guidelines, there has been a decrease in the use of elective colectomy following an episode of diverticulitis.

5.2 Introduction

Patients with a history of diverticulitis managed non-operatively may be considered for interval elective colectomy, with the goal of preventing subsequent disease recurrence, emergency surgery and colostomy. Traditionally, elective colectomy has been recommended for young patients (<50 years at initial presentation), patients who have had one complicated disease
episode (abscess, fistula, perforation), and patients who have experienced two episodes of uncomplicated diverticulitis$^{131,201}$.

However, there is increasing evidence suggesting that the natural history of the disease is benign and that few patients will go on to experience complicated recurrence requiring emergency operation, leading many to challenge the traditional indications for elective surgery$^{68,135,138,143,154-157}$. These data are reflected in more contemporary practice guidelines that favor individualized treatment decisions and more selective use of elective colectomy$^{53}$. Despite these changing recommendations, results of studies exploring trends in the rates of elective colectomy for diverticulitis have been mixed, with some studies actually demonstrating a paradoxical increase in rates of elective surgery$^{33,89,118,180}$.

The objectives of this study were to (a) characterize the surgical approaches and clinical outcomes associated with elective colectomy for diverticulitis, and (b) evaluate temporal trends in the use of elective colectomy following initial non-operative management of colonic diverticulitis.

### 5.3 Methods

**Study Design**

This was a population-based retrospective cohort study evaluating trends in the use of elective colectomy over 2002-2012 for patients who have had at least one episode of acute diverticulitis initially treated without surgery. This cohort has been previously described in other publications focusing on the management of acute diverticulitis and the clinical course of the disease (Li et al, DCM, manuscript submitted for publication; Li et al, Annals of Surgery, in
press). This study was approved by the Research Ethics Board at the Sunnybrook Health Sciences Centre.

Data Sources

Data were obtained from administrative health databases from the province of Ontario, Canada, which are maintained and analyzed at the Institute of Clinical Evaluative Sciences, Toronto, Ontario. The Canadian Institute of Health Information (CIHI) Discharge Abstract Database (DAD) uses codes from the International Classification of Disease, Tenth Revision-Canada (ICD-10-CA), and provides demographic information, diagnoses, interventions, and discharge information for all hospitalizations in the province. The National Ambulatory Care Reporting System (NACRS) provided information on all Emergency Department (ED) visits in the province. Dates of death were obtained from the Registered Persons Database (RPDB). Linkage of datasets was accomplished using an encrypted unique patient identifier.

Cohort

The ICD-10-CA diagnosis codes K57.2 and K57.3 (diverticulitis of the large intestine, with and without perforation or abscess) were used to identify all Ontario residents 18 years of age or older who were admitted through any Emergency Department with a principal diagnosis of acute colonic diverticulitis from April 1, 2002 to March 31, 2012. To limit the cohort to patients with an incident diagnosis of diverticulitis, patients who had any previous hospital admissions or ED visits for colonic diverticulitis were excluded, dating back to the start of these administrative databases (1988 for hospital admissions, 2000 for ED visits). Patients with concurrent gastrointestinal bleeding, or any history of colorectal cancer or colectomy were also excluded (for relevant codes, see Appendix). Patients who were discharged from hospital without
any operative intervention, and who had at least 30 days of follow-up, comprised the final study cohort.

**Covariates**

The relationship between calendar year and rates of elective colectomy might be confounded by changes in patient characteristics over time. We considered as potential confounders: baseline patient characteristics including age, sex, medical comorbidity burden, neighborhood income quintile, and rural residency, as well as disease factors (early readmission, index disease severity). The Deyo adaptation of the Charlson Comorbidity Index (CCI) was used to quantitate the comorbidity burden and was calculated from administrative discharge data in the one year prior to index admission. Income quintile was derived using median neighborhood (dissemination area) household income by postal code and Canadian census data. Residency was classified as urban or rural based on postal code, with urban residency being defined as residing within a Census Metropolitan Area or Census Agglomeration with an urban core > 10,000 people (Statistics Canada). Early readmission was defined as urgent hospital readmission for acute diverticulitis within one year of discharge. Index disease severity was classified as uncomplicated (ICD-10-CA code K57.3, diverticulitis of the large intestine without perforation or abscess), complicated without percutaneous abscess drainage (ICD-10-CA code K57.2, diverticulitis of the large intestine with perforation or abscess), or complicated with percutaneous abscess drainage (ICD-10-CA code K57.2 with procedure code for percutaneous abscess drainage) (Appendix).

**Outcomes**
Elective colectomy was identified by an elective hospital admission for a principal diagnosis of acute colonic diverticulitis with an ICD-10-CA procedure code for any colectomy. Specific operative strategies used in elective surgery (laparoscopy and bowel exteriorization) were identified using ICD-10-CA intervention codes (Appendix). In-hospital mortality and hospital length of stay (LOS) were also evaluated. We censored events occurring within the first 30 days after discharge, as operations taking place within this early interval were more likely to reflect persistent index disease. Thus observation began at 30 days post-discharge for all patients. Follow-up continued for all patients until elective colectomy was performed, or until occurrence of a competing event (emergency operation for diverticulitis, all-cause mortality), or end of the study follow-up period (March 31, 2012).

Statistical Analysis

Statistical analyses were performed using SAS, version 9.3 (SAS Institute, Cary, North Carolina). Categorical variables were compared using the Pearson $\chi^2$ test and continuous variables were compared using Wilcoxon rank sum test or Kruskal-Wallis test. All tests were two sided and $p$-values less than 0.05 were considered statistically significant.

Time to event analysis was performed and the cumulative incidence of elective surgery at various time points following discharge was estimated. Unlike the commonly-used Kaplan – Meier method which censors for competing events, a cumulative incidence approach explicitly accounts for the competing events of death and emergency operation\textsuperscript{189}. Stratified analyses were performed by age group (age < 50 years at first presentation versus age $\geq$ 50 years) and disease severity (uncomplicated diverticulitis, complicated disease without percutaneous abscess drainage, complicated disease with percutaneous abscess drainage). Gray’s modified log-rank
test was used to compare unadjusted incidence estimates and evaluate the equality of cumulative incidence curves.

To evaluate temporal changes in the use of elective colectomy, the proportion of admitted patients undergoing elective operative intervention within one year of discharge was calculated for each calendar year. Trends in operative strategy (use of laparoscopy and bowel exteriorization) were evaluated as well. Cochran-Armitage was used to test for trends over time. Multivariable logistic regression with generalized estimating equations (GEE) was used to adjust for changes in patient and disease characteristics while determining the effect of time (calendar year) on the use of elective colectomy for diverticulitis. GEE was used to account for potential clustering of patients at hospital sites. Adjusted odds ratios with 95% confidence intervals are reported.

5.4 Results

A total of 18,543 patients were admitted with their first episode of acute diverticulitis from 2002-2012, of which 14,545 (78.4%) were managed non-operatively. An additional 421 patients were excluded for undergoing colectomy within 30 days or for having less than 30 days of follow-up, leaving 14,124 patients (76.2%) who remained eligible for elective colectomy, comprising the final study cohort with a median follow-up interval of 3.9 years (minimum 30 days, maximum 10 years, IQR: 1.7-6.4 years).

Among this cohort, a total of 252 (1.8%) patients underwent emergency surgery for recurrent diverticulitis, and 1,781 (12.6%) patients died without any operative (urgent or elective) intervention for diverticulitis. Overall, 1,342 patients (9.5%) underwent elective colectomy during follow-up (table 1). Patients who underwent elective colectomy were younger,
had less medical comorbidity, higher income, more severe index disease, and were more likely to have experienced an early recurrence (table 1). Of the 1,342 patients who underwent elective surgery during follow-up, 1,108 (82.6%) experienced only the index admission prior to elective surgery, 197 (14.7%) had 2 admissions for diverticulitis prior to elective colectomy, and 37 (2.8%) had 3 or more admissions prior to surgery.

**Time to event analysis**

While accounting for the competing events of death and emergency operation, the cumulative incidence of elective colectomy was 7.6% at 1 year post-discharge, 10.2% at 5 years, and 11.3% at 10 years. Among patients who underwent elective surgery during follow-up, the median time from discharge to elective surgery was 139 days (IQR: 64-335); 76.8% underwent elective surgery within the first year following discharge, and 88.2% within 2 years after discharge. Cumulative incidences of elective surgery are presented in figure 2, stratified by age group and severity of index disease. In unadjusted analysis, younger patients (< 50 years) and those with more severe disease at index admission were more likely to undergo elective colectomy.

**Clinical outcomes and operative approaches**

Elective colectomy was associated with low in-hospital mortality (0.2%), median LOS was 6 days (IQR: 5-8 days), and 7.5% received either an ileostomy or colostomy. The risk of ostomy creation did not differ based on severity of the index disease (p=0.36). Use of ileostomy/colostomy fluctuated annually from 2.5% to 11.1% of elective operations, although there was a general trend towards increased use over time (Cochran-Armitage test for trend p=0.034).
Laparoscopic colectomy was performed in 33.4% of patients undergoing surgery. Patients who had complicated index disease requiring percutaneous drainage were less likely to undergo laparoscopic elective surgery (22.0%), compared to patients who had uncomplicated disease (34.7%) and complicated disease without percutaneous drainage (33.8%) (p=0.03). Use of laparoscopy increased over time, from 17.3% of elective operations in 2002 to 45.1% in 2011 (Cochran-Armitage test for trend p<0.001).

**Temporal trends in the use of elective colectomy**

We evaluated trends in rates of elective colectomy over 2002-2012 for patients admitted with diverticulitis and managed non-operatively, by focusing on those patients who underwent operation within the first year of their index admission as the majority of procedures are done within this time interval. Taking this approach, patients with less than one year of follow-up were excluded, leaving 12,600 patients for analysis, of whom 953/12,600 (7.6%) underwent elective operation within one year of index admission.

The proportion of patients undergoing elective colectomy declined over time, from 9.6% of patients admitted in 2002 to 3.9% by 2011 (Cochran-Armitage test for trend, p<0.001) (figure 2). The decline in elective surgery was most pronounced in younger patients < 50 years (16.0% of young patients treated in 2002 underwent elective surgery, decreasing to 5.4% in 2011), and in patients with complicated index disease (27.4% of patients in 2002 to 6.9% in 2011) (all p<0.001). For patients who had complicated disease requiring percutaneous abscess drainage at index admission, the proportion undergoing elective surgery within one year of discharge decreased from 35.7% in 2002 to 11.8% in 2011, although this trend did not reach statistical significance due to small sample size (p=0.28). There was a more modest decline in elective
surgery rates for patients with uncomplicated disease (7.0% in 2002 to 2.6% in 2011, p<0.001), and for patients 50 years of age or older (7.4% in 2002 to 3.3% in 2011, p=0.09).

In multivariable regression, younger age, lower burden of medical comorbidity, greater severity of index disease, and early disease recurrence were associated with increased likelihood of undergoing elective colectomy within one year of discharge (table 2). After adjusting for changes in patient and disease characteristics over time, the odds of elective surgery decreased by 0.92 per annum (adjusted OR 95% CI: 0.89-0.95).

5.5 Discussion

We have demonstrated a significant decline in the use of elective colectomy for diverticulitis over the past decade. In this cohort, the proportion of patients undergoing elective colectomy within 1 year of discharge declined from 9.6% of patients admitted in 2002 to 3.9% by 2011. Consistent with accruing evidence and evolving practice guidelines\textsuperscript{53, 148}, the observed decrease in elective surgery was most pronounced for patients younger than 50 years of age and those with complicated disease. When elective surgery is performed, use of laparoscopy has increased, with nearly half of elective operations being performed laparoscopically by 2011. While elective colectomy for diverticulitis is associated with low mortality (0.2%), it is associated with significant stoma morbidity (7.5%).

Young age at first presentation has been hypothesized to be a risk factor for more virulent disease, and earlier guidelines have recommended elective colectomy for patients less than 50 years of age\textsuperscript{131, 202}. However, increasing evidence has accumulated to contradict this theory\textsuperscript{135, 137, 138}. Two recent meta-analyses suggest younger patients are at increased risk of disease recurrence\textsuperscript{141, 142}, but the relationship between age and risk of emergency operation remains
unclear. Whereas Katz et al.\textsuperscript{142} found no significant association between young age and risk of emergency operation following initial non-operative management, van de Wall et al.\textsuperscript{141} reported a pooled relative risk of 1.46 for emergency surgery (95% CI: 1.29-1.66)\textsuperscript{141}. However, the absolute risk difference observed was small (7.3% vs 4.9%)\textsuperscript{141}, and was highly influenced by the results of one population-based study\textsuperscript{141}. In our prior work, we did not find any association between young age and risk of emergency operation at index presentation or during follow-up after initial non-operative management (Li et al, Dis Colon Rectum, 2014; Li et al, Annals of Surgery, 2014). Taken together, young age does not appear to confer a more virulent disease trajectory\textsuperscript{135, 138}, leading to the recommendations to discourage the practice of elective surgical resection based on age criteria alone\textsuperscript{52, 53}. These guidelines and the data upon which they have been developed are slowly being translated into practice as evidenced by the reduction in rates of elective surgery in this population.

Complicated diverticulitis accounts for 20-30\% of cases of diverticulitis\textsuperscript{31}, yet little is known about the clinical course of such patients managed without operation. Practice guidelines have traditionally recommended elective colectomy following non-operative management of complicated diverticulitis\textsuperscript{53, 131}, supported by evidence suggesting that such patients are at increased risk of recurrent disease and sepsis\textsuperscript{54, 57, 124}. However, the risk of subsequent disease-related events in this subset of patients has not been well studied, with data limited to a few single or multi-institution cohort studies with small sample sizes and high loss to follow-up\textsuperscript{148}, with reported recurrence rates ranging from 24\% to 53\%\textsuperscript{15, 57, 127, 143, 148}. More recently, the success of managing complicated diverticulitis without elective colectomy has led some to question the necessity of routine elective surgery, particularly in patients at high operative risk\textsuperscript{68, 86, 143, 146}. In our prior work, the 5-year cumulative incidence of readmission and emergency
surgery was only 12.0% and 4.3% respectively among patients with complicated diverticulitis (Li et al, Annals of Surgery, in press). These data suggest routine elective colectomy may not be necessary for many patients with complicated disease and has likely influenced the decline in rates of elective surgery demonstrated in the current study.

In this study cohort, early readmission within one year of discharge was associated with elective colectomy, although the majority (83%) of patients undergoing elective colectomy experienced only one admission prior to surgery. Recurrent disease has traditionally been an indication for elective colectomy\textsuperscript{131, 201}, but there is increasing evidence to challenge the hypothesis that patients with recurrent disease are at increased risk of adverse events\textsuperscript{126, 154, 155}, with some observing the index presentation may carry the highest risk of perforation\textsuperscript{154, 156, 157}. Decision analysis has been used to determine the optimal number of recurrences before elective surgery, and elective colectomy was found to be most cost effective when performed after 3-4 episodes\textsuperscript{159, 160}. However, studies have demonstrated that elective surgery is associated with improved quality of life\textsuperscript{177}, as well as lower need for further physician treatment, readmission and LLQ abdominal pain\textsuperscript{178}. At present, the optimal decision making around elective colectomy for patients with recurrent disease remains unclear; current guidelines recommend individualized management strategies based on the severity of prior episodes, the presence of persistent or chronic symptoms, quality of life, and general medical condition of the patient\textsuperscript{52}.

The operative risks associated with elective surgery must be considered in clinical decision making. In the current study, the in-hospital mortality was low at 0.2%; however, a significant proportion (7.5%) of patients undergoing elective surgery following diverticulitis received either an ileostomy or colostomy. Elective colectomy for diverticular disease has been observed to carry greater morbidity and mortality than colon resection for cancer\textsuperscript{168, 169}, with
previously reported rates of mortality and morbidity as high as 0.4%-2% and 26-30% respectively. The proportion of patients receiving an ostomy during elective colectomy for diverticulitis has been reported to be as high as 15% in some cohorts. Furthermore, as many as 10% of patients undergoing elective resection go on to experience recurrent diverticulitis, of whom up to 3.4% require further surgery, and persistent symptoms may be found in up to 27% of patients. These data suggest that elective colectomy following diverticulitis is associated with significant morbidity. Further studies are needed to determine if the benefits of elective colectomy are able to outweigh the risks. Results from randomized trials comparing non-operative versus operative management for persistent or recurrent diverticulitis in reducing mortality, morbidity, quality of life, and total costs may add new knowledge to better inform treatment decisions.

Limitations in our study are related to its observational design. Selection bias may exist as patients offered elective colectomy likely differ systematically from those not offered elective colectomy - for example, with regards to operative risk and risk of receiving ostomy. This limitation suggests that the operative mortality rate and ostomy rate observed in our cohort may not be applicable to other populations, such as older patients, those with greater medical comorbidity, and those with uncomplicated index disease. There is also potential for bias due to exclusion of patients with less than one year of follow-up available from the analysis of temporal trends; for example, due to death within one year of discharge. However, there is no reason to suspect that a greater proportion of patients are dying within one year over the decade of observation, or that the characteristics of excluded patients have changed over time. Other study limitations are related to the use of administrative health databases. Specifically, administrative health records lack detailed clinical information, limiting the ability to adjust for potential
confounders and the ability to identify the indication for elective surgery for individual patients. The study may also be limited by inaccuracies in *ICD-10-CA* diagnostic and procedural codes within the discharge database, although previous studies have demonstrated good accuracy in coding within discharge records\textsuperscript{181-183}. Finally, the current study did not evaluate the later effects of reduced use of elective surgery. It is possible that decreased use of elective prophylactic colectomy for patients with known risk factors may lead to increased incidence of subsequent recurrences and perforated disease requiring emergency colectomy/colostomy. However, prior reports have not found such an association\textsuperscript{34}.

In summary, our study has demonstrated a significant decrease in the use of elective colectomy following diverticulitis, particularly for young patients and those with complicated index disease. This is consistent with growing consensus that the natural history of diverticulitis is typically benign and that elective colectomy may not be necessary for the majority of patients. Contemporary guidelines suggest an individualized and conservative approach in selecting patients for elective surgery. To determine which patients truly benefit from elective surgery, future research should aim to compare the risks and benefits of elective colectomy against conservative management for high risk patient subgroups, such as patients with multiple recurrent episodes, persistent abdominal symptoms, high risk medical comorbidities, and those with large, pelvic abscesses\textsuperscript{86, 143, 152}. Specific focus should be aimed at comparing elective surgery to non-operative management in the outcomes of reducing disease related morbidity and mortality, reducing healthcare utilization, and improving patient quality of life.
### 5.6 Tables for Chapter 5

**Table 5.6.1** - Baseline patient characteristics, comparing those undergoing elective surgery and those not undergoing elective surgery during the follow-up period

<table>
<thead>
<tr>
<th>Patient &amp; Disease Characteristics</th>
<th>All patients at index episode (n=14,124) N (%)</th>
<th>Patients undergoing elective colectomy (n=1,342) N (%)</th>
<th>Patients not undergoing elective colectomy (n=12,782) N (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age - Median (IQR)</strong></td>
<td>59 (48-74)</td>
<td>51 (44-61)</td>
<td>60 (48-75)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female</td>
<td>7,466 (52.9)</td>
<td>642 (47.8)</td>
<td>6,824 (53.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Charlson Comorbidity Score</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>0</td>
<td>11,012 (78.0)</td>
<td>1,203 (89.6)</td>
<td>9,809 (76.7)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1,665 (11.8)</td>
<td>95 (7.1)</td>
<td>1,570 (12.3)</td>
<td></td>
</tr>
<tr>
<td>2+</td>
<td>1,447 (10.2)</td>
<td>44 (3.3)</td>
<td>1,403 (11.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Patient income quintile</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.006</td>
</tr>
<tr>
<td>Lowest quintile</td>
<td>2,673 (18.9)</td>
<td>233 (17.4)</td>
<td>2,440 (19.1)</td>
<td></td>
</tr>
<tr>
<td>Second quintile</td>
<td>2,927 (20.7)</td>
<td>283 (21.1)</td>
<td>2,644 (20.7)</td>
<td></td>
</tr>
<tr>
<td>Third quintile</td>
<td>2,785 (19.7)</td>
<td>229 (17.1)</td>
<td>2,556 (20.0)</td>
<td></td>
</tr>
<tr>
<td>Fourth quintile</td>
<td>2,803 (19.9)</td>
<td>303 (22.6)</td>
<td>2,500 (19.6)</td>
<td></td>
</tr>
<tr>
<td>Highest quintile</td>
<td>2,892 (20.5)</td>
<td>294 (21.9)</td>
<td>2,598 (20.3)</td>
<td></td>
</tr>
<tr>
<td><strong>Location of residence</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.94</td>
</tr>
<tr>
<td>Urban</td>
<td>12,268 (86.9)</td>
<td>1,167 (87.0)</td>
<td>11,101 (86.9)</td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>1,850 (13.1)</td>
<td>175 (13.0)</td>
<td>1,675 (13.1)</td>
<td></td>
</tr>
<tr>
<td><strong>Disease severity at index admission</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Uncomplicated</td>
<td>11,172 (79.1)</td>
<td>792 (59.0)</td>
<td>10,380 (81.2)</td>
<td></td>
</tr>
<tr>
<td>Complicated, no abscess drain</td>
<td>2,543 (18.0)</td>
<td>441 (32.9)</td>
<td>2,102 (16.5)</td>
<td></td>
</tr>
<tr>
<td>Complicated, with abscess drain</td>
<td>409 (2.9)</td>
<td>109 (8.1)</td>
<td>300 (2.4)</td>
<td></td>
</tr>
<tr>
<td><strong>Early hospital readmission a</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No</td>
<td>13,492 (95.5)</td>
<td>1,192 (88.8)</td>
<td>12,300 (96.2)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>632 (4.5)</td>
<td>150 (11.2)</td>
<td>482 (3.8)</td>
<td></td>
</tr>
</tbody>
</table>

*a Early hospital readmission is defined as urgent hospitalization for recurrent diverticulitis within 1 year of discharge.
Table 5.6.2 - Patient characteristics associated with elective colectomy within 1 year of discharge*

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Adjusted Odds Ratio of Elective Surgery (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 5 year increase)</td>
<td>0.88 (0.86-0.90)</td>
</tr>
<tr>
<td>Female Sex</td>
<td>1.05 (0.92-1.19)</td>
</tr>
<tr>
<td>Charlson Comorbidity Index (per 1 point increase)</td>
<td>0.73 (0.64-0.84)</td>
</tr>
<tr>
<td>Patient income quintile by postal code</td>
<td></td>
</tr>
<tr>
<td>Lowest quintile (reference)</td>
<td>-</td>
</tr>
<tr>
<td>Second quintile</td>
<td>1.09 (0.90-1.32)</td>
</tr>
<tr>
<td>Third quintile</td>
<td>0.89 (0.72-1.10)</td>
</tr>
<tr>
<td>Fourth quintile</td>
<td>1.19 (1.01-1.40)</td>
</tr>
<tr>
<td>Highest quintile</td>
<td>1.13 (0.91-1.40)</td>
</tr>
<tr>
<td>Rural Residency</td>
<td>1.04 (0.85-1.28)</td>
</tr>
<tr>
<td>Classification of disease:</td>
<td></td>
</tr>
<tr>
<td>Uncomplicated diverticulitis (reference)</td>
<td>-</td>
</tr>
<tr>
<td>Complicated diverticulitis, no abscess drain</td>
<td>3.23 (2.70-3.86)</td>
</tr>
<tr>
<td>Complicated diverticulitis, with abscess drain</td>
<td>7.37 (5.49-9.91)</td>
</tr>
<tr>
<td>Urgent readmission in first year post discharge</td>
<td>2.43 (1.92-3.08)</td>
</tr>
<tr>
<td>Calendar Year of Index Admission</td>
<td>0.92 (0.89-0.95)</td>
</tr>
</tbody>
</table>

*Logistic regression with generalized estimating equations
5.7 Figures for Chapter 5

Figure 5.7.1 - Cumulative incidence of elective surgery following discharge, by (a) age group, (b) severity of index disease.
Figure 5.7.2 - Trends (unadjusted) in rate of elective colectomy following initial non-operative management, 2002-2011
Chapter 6
Conclusions, Limitations & Future Directions

6.1 Thesis Summary

In objective #1, temporal changes in the management of acute diverticulitis were characterized. Retrospective analysis of a cohort of 18,543 patients admitted for a first episode of acute diverticulitis from 2002 to 2012 revealed a significant decrease in the proportion of patients undergoing urgent operation, from 28% of admitted patients in 2002 to 16% in 2012. This decline in operative intervention occurred despite an increase in the proportion of patients admitted with complicated disease, rising from 32% of admissions in 2002 to 38% in 2012. In our cohort, almost all patients with uncomplicated disease, and half of patients with complicated disease, were successfully managed non-operatively. Use of percutaneous abscess drainage also increased from 1.9% of admissions in 2002 to 3.3% in 2012. After adjusting for changes in patient characteristics and disease severity over time, the odds of urgent operation decreased by 0.87 per annum (95% CI: 0.85-0.89).

When urgent operative intervention was necessary, temporal changes in the operative strategies used were observed. Of the 3,873 patients undergoing urgent surgery between 2002 and 2012, use of laparoscopy increased (from 9% of urgent operations to 18%, p<0.001), while use of Hartmann’s remained unchanged (64% of all urgent operations for diverticulitis). Despite the increase in use of non-operative and minimally invasive treatment strategies for increasingly
complicated disease, there was no observed worsening of patient outcomes over this period. During this time, in-hospital mortality decreased significantly (from 2.7% in 2002 to 1.9% in 2012), as did median length of stay (from 5 days, IQR 3-9, to 3 days, IQR 2-6) (all p<0.001).

In objective #2, the clinical course of the disease was characterized for patients following non-operative management of a first episode of diverticulitis. Of the 18,543 patients in the study cohort, 14,124 were successfully managed non-operatively and had at least 30 days of follow-up available. These 14,124 patients were followed for a median of 3.9 years (maximum 10, IQR 1.7-6.4) to determine the risk of readmission and emergency operation for recurrent diverticulitis. The 5-year cumulative incidence of readmission was 9.0%, while 5-year cumulative incidence of emergency surgery for recurrent diverticulitis was only 1.9%. By comparison, patients were much more likely to die from other causes at 5 years of follow-up (cumulative incidence 14.1%) than to experience any further disease events. At 5 years of follow-up, patients age <50 years had higher incidence of readmission than patients age ≥50 (10.5% vs 8.4%, p<0.001) but not emergency surgery (1.8% vs 2.0%, p=0.52). Patients with complicated disease (abscess, perforation) were at increased risk of readmission than those with uncomplicated disease (12.0% vs 8.2%, p<0.001), as well as increased risk of emergency surgery (4.3% vs 1.4%, p<0.001). In multivariable regression, complicated disease and number of prior admissions were associated with increased risk of emergency surgery, yet age <50 years was not. Notably, risks associated with complicated disease were non-proportional over time, being highest immediately following discharge and decreasing thereafter.

In objective #3, we evaluated clinical outcomes and temporal trends in the use of elective colectomy following successful non-operative management of colonic diverticulitis. Again, a total of 14,124 patients in our cohort were successfully managed non-operatively for a first
episode of acute diverticulitis and had at least 30 days of follow-up, making them eligible for interval elective colectomy. Median follow-up was 3.9 years [maximum 10, interquartile range (IQR) 1.7-6.4]. Overall, 1,342 (9.5%) patients in this cohort underwent elective colectomy, of which 33% were performed laparoscopically and 7.5% had an associated ostomy. In-hospital mortality associated with elective colectomy was low at 0.2%. The majority (76%) of elective operations were performed within 1 year of discharge from the index disease episode (median 160 days from discharge to elective surgery, IQR 88-346).

Over the decade of observation, there was a significant trend towards reduced use of interval elective colectomy following successful non-operative management of diverticulitis. The proportion of patients undergoing interval elective colectomy within 1 year of discharge declined from 9.6% of discharged patients in 2002 to 3.9% by 2011 (p<0.001). The decline was most pronounced in patients <50 years of age (from 17% to 5%), and in patients with complicated disease (from 28% to 8%) (all p<0.001). In multivariable regression, younger age, lower medical comorbidity, complicated disease, and early readmission were associated with elective colectomy. After adjusting for changes in patient characteristics and disease severity over time, the odds of elective surgery decreased by 0.93 per annum (adjusted OR 95% CI: 0.90-0.95). Consistent with evolving practice guidelines and accumulating evidence for the benign natural history of the disease, there has been a decrease in the use of interval elective colectomy following successful non-operative management of diverticulitis.
6.2 Implications

The results of this population based study offer new knowledge that can be used to aid in the decision making in managing patients with this common condition. First, we have demonstrated the natural history of the disease to be characteristically benign. Our data suggest that readmission and emergency operation for recurrent diverticulitis are rare complications following initial successful non-operative management of diverticulitis. This clinical trajectory remains true even for patients with traditional risk factors such as young age and complicated index disease. Taken together, our results suggest that elective prophylactic colectomy may be unwarranted for the majority of patients who have had an episode of diverticulitis managed non-operatively, and has no role in preventing emergency surgery for diverticulitis. This evidence supports a selective and individualized approach to use of elective colectomy following diverticulitis, and lends further support for the practice of deferring elective colectomy for patients without persistent chronic symptoms or multiple frequent recurrences. The indications for elective surgery should be focused on ongoing symptomology, frequency and number of prior episodes, and patient quality of life, with age at first presentation and the severity of prior episodes being less significant considerations.

Second, we have demonstrated significant practice changes in the management of colonic diverticulitis over the past decade. The proportion of patients undergoing urgent operative intervention for acute diverticulitis has decreased over time, in spite of the greater frequency of complicated disease. These changes were most evident in younger patients and those presenting with complicated disease. Several factors might account for these observations. Improved diagnostic accuracy with more frequent use of cross-sectional imaging, better supportive care (including earlier and broader spectrum antimicrobials) and more aggressive approaches to
image-guided percutaneous abscess drainage all might increase the probability of successful non-operative management. The more pronounced decline in urgent operative intervention for young patients and those with complicated disease is reflective of evolving surgeon preferences and national practice guidelines. Importantly, mortality rates and length of stay in hospital have decreased over this same time period, suggesting that increased use of non-operative management strategies are safe and have not resulted in adverse clinical outcomes in patients. While observational studies cannot compare the safety and efficacy of various treatment strategies, the results of this study suggest that non-operative management is being increasingly utilized for acute diverticulitis while patient outcomes have improved. Whether these changes might lead to higher rates of recurrence and greater resource utilization over prolonged follow-up will need to be evaluated.

When operative intervention is required, the use of laparoscopic approaches has doubled over 2002-2012. A greater spectrum of surgical options with increasing evidence of efficacy has challenged traditional operative strategies for acute diverticulitis. While other investigators have reported rates of laparoscopic colectomy in the emergency setting in the range of 2.8%-7.8%, the higher observed rates of laparoscopy use in this cohort might relate to our broader definition of laparoscopic surgery to include diagnostic laparoscopy, laparoscopic lavage, laparoscopic resection or Hartmann’s procedure, as well as regional specific financial incentives for this approach. Despite the lack of level I evidence to support the use of laparoscopy for emergency diverticulitis surgery, its use will likely continue to increase as surgeons develop greater expertise with such techniques in the elective setting and as more evidence accrues supporting its safety and efficacy.
Interestingly, Hartmann’s procedure has remained the most frequently employed operative strategy in the emergency setting, with little to no change over the past decade. Notably, the proportion of admitted patients undergoing urgent operative intervention decreased over time despite an increase in the proportion of patients admitted with complicated disease, suggesting surgeons are reserving urgent operation for patients with increasingly severe disease and appropriately using Hartmann’s procedure for a sicker population of patients. Whether the continued popularity of Hartmann’s procedure is due to the increasing clinical severity of patients undergoing urgent operation, or whether it is due to surgeon discomfort with creating an anastomosis in the setting of intra-abdominal infection, is unclear from the present study. Despite increasing interest in the use of primary anastomosis for acute complicated diverticulitis, the evidence to support its safety remains lacking. Numerous observational studies have been published reporting favorable outcomes for primary anastomosis in comparison to Hartmann’s procedure, but these studies are subject to significant selection bias, and there remain few prospective or randomized studies reported to date. Clearly, further evidence from randomized trials is needed before primary anastomosis in the setting of acute diverticulitis gains greater acceptance and popularity in use.

Finally, we have demonstrated a significant decline in the use of elective colectomy following successful non-operative management of diverticulitis over the past decade. In this cohort, the proportion of patients undergoing elective colectomy within 1 year of discharge declined from 9.6% of patients admitted in 2002 to 3.9% by 2011. The observed decrease in elective surgery was most pronounced for patients younger than 50 years of age and for those with complicated disease, which is consistent with accruing evidence that the clinical course of such patients may be more benign than previously described. When elective surgery is
performed, use of laparoscopy has increased, with nearly half of elective operations being performed laparoscopically by 2011. Furthermore, we have demonstrated that while elective colectomy is associated with low perioperative mortality, the risk of ostomy remains significant at 7.5%, and requires substantial health resource utilization with a median length of stay in hospital of 6 days. Taken together, it appears that accruing evidence and changes in practice guidelines are likely to lead to increasing favor of non-operative management for patients with diverticular disease, with elective surgery being reserved only for very select patients with persistent chronic symptoms or frequent attacks impeding on quality of life. Again, the impact of such practice changes on long term rates of readmission and resource utilization will need to be evaluated.

6.3 Limitations

6.3.1 Limitations associated with use of administrative health data

Administrative datasets have the unique advantage of providing information for entire populations with minimal loss to follow-up, but its use also confers several limitations that must be taken into consideration in interpreting our results. As the data are not collected specifically for research purposes, administrative health data lack detailed clinical information, such as severity of disease and degree of physiological derangement, as well as information on patient factors, such as ethnicity, that may be associated with the outcome of interest. This limits the variables available for risk adjustment and allows for the possibility of residual confounding.

Administrative data may also be limited by misclassification and potential inaccuracies in the diagnosis and intervention codes. For example, subsequent complications such as gastrointestinal bleeding, fistula, or bowel obstruction that occur during the follow-up period but
are not specified with a primary diagnosis code for diverticulitis would not be captured in the analysis, which might lead to an underestimation of complication rates during follow-up. Furthermore, assumptions must be made in the interpretation of administrative records which may be inaccurate. For example, we have assumed that any operation that takes place during an urgent readmission for diverticulitis represents an emergency operation in response to complicated or perforated recurrent disease. In reality, a proportion of such operations may actually have been elective or semi-urgent in nature, in response to patient or surgeon preference to operate on patients who are traditionally thought to be at high risk for subsequent events. However, such an error would actually lead to a conservative overestimate of the risk of subsequent emergency operation for our cohort, lending further support to our conclusions. Furthermore, prior reports have demonstrated a high degree of accuracy in administrative discharge data when compared to chart abstraction, with 84% agreement in the diagnosis of diverticulitis, and 97% agreement in intervention codes\textsuperscript{181-183}.

Finally, patient-reported factors such as ongoing symptomology and reduced quality of life are not captured within administrative records, but represent important clinical outcomes and frequent indications for operative intervention.

6.3.2 Lack of follow-up data

It is possible that increased use of non-operative management strategies during the index admission in conjunction with declining use of elective colectomy following the acute episode may lead to an increased risk of disease recurrence and emergency surgery in the study population in the future. This may also be associated with increasing healthcare resource utilization and costs. Published reports have not demonstrated such an association, suggesting
this effect is unlikely. This possibility is out of the scope of the present study and was not explored, but represents an important outcome that should be evaluated in future studies.

6.3.3 Readmission versus disease recurrence

Readmission for recurrent diverticulitis was selected as the outcome of interest rather than disease recurrence, which may include milder episodes that are successfully treated in the outpatient setting. This approach is consistent with the methodology used in other studies derived from population-level or administrative health data, but leads to an underestimate of the disease recurrence rate, as many patients might be successfully managed in the outpatient setting. Indeed, when we included all outpatient and ambulatory clinic visits coded with a diagnosis of diverticulitis, the proportion of patients experiencing disease recurrence increased from 8% of the cohort to 21%. We elected to exclude outpatient records due to the challenges in rendering a diagnosis of diverticulitis in the ambulatory setting, as many patients with a documented history of diverticular disease might receive a diagnosis and empiric antibiotics for symptoms without confirmatory investigations. The accuracy of outpatient diagnosis codes have been questioned by those using administrative data for research, and reports have demonstrated lower accuracy for diagnostic codes obtained from outpatient data compared to inpatient data. For example, in one validation study, the positive predictive value of diverticulitis diagnosis codes was 97% in inpatient administrative records, compared to only 76% in outpatient records. Taken together, the true rate of disease recurrence likely lies above 8% and below 21%, but given the concerns of inaccuracy in outpatient administrative records, we have chosen to restrict our analysis to hospital readmissions only. Therefore, our study results should not be interpreted as estimating the overall risk of disease recurrence or recurrent symptoms, as our objective was
only to estimate the risk of experiencing clinically significant recurrence that requires readmission or urgent operation.

6.3.4 Potential for selection bias and confounding by indication

As with all observational studies, the role of selection bias and confounding by indication cannot be excluded. Results may be biased if patients who are at the highest risk for readmission and emergency surgery are preferentially selected by surgeons to undergo elective colectomy. However, only 9.5% of the cohort underwent elective surgery during follow-up. Using a conservative estimate, even if half of these patients would have experienced subsequent disease events without elective surgery the estimated overall incidences of readmission and emergency operation in the cohort would only approach 15% and 7% respectively, making it unlikely that selection bias has significantly changed the conclusions drawn from this study.

6.4 Future Directions

6.4.1 Operative approaches for acute complicated diverticulitis

Despite the increasing interest in minimally-invasive operative approaches in treating acute diverticulitis, there is limited evidence available to support the use of laparoscopic and non-resectional strategies. To date, reports supporting laparoscopic lavage for Hinchey III disease have been based only on observational cohort studies or case series, no randomized trials have been reported. Interestingly, the LOLA arm of the LADIES trial comparing laparoscopic lavage to resection for Hinchey III disease was closed prematurely by the study’s data safety monitoring board, and although detailed results have yet to be published, the authors of that study concluded that laparoscopic lavage was not superior to resection for treatment of
generalized peritonitis due to perforated diverticulitis. Laparoscopic resection has been demonstrated to provide benefits over open resection in elective surgery for diverticular disease, including decreased postoperative pain, fewer postoperative complications, less postoperative ileus, and shorter length of stay\textsuperscript{117}. However, there is no evidence to support the use of laparoscopic resection over open resection in the urgent setting for perforated diverticulitis\textsuperscript{119,120}. Future research should be aimed at identifying the best operative approach for patients with complicated or perforated diverticulitis requiring emergency operation, to determine if minimally invasive approaches such as laparoscopic lavage, laparoscopic resection, and laparoscopic Hartmann’s procedure are safe in the emergency setting and if they offer benefits over open approaches. Aside from differences in mortality and morbidity, future trials should also focus on important clinical outcomes such as postoperative pain, return of bowel function, return to work, length of stay in hospital, and associated complications such as rates of incisional hernia and adhesive bowel obstruction. Further randomized trials and prospective studies of these emerging management strategies will help to guide future treatment recommendations.

Several reports have provided evidence that primary resection and anastomosis, with or without diverting ileostomy, is a safe alternative to Hartmann’s procedure in selected patients with diverticulitis requiring urgent operation. These reports suggest that primary anastomosis is associated with higher stoma reversal, fewer serious complications, shorter length of stay, and lower hospital costs\textsuperscript{105}. However, the bulk of evidence relating to the safety of primary anastomosis in this setting is derived from retrospective case series with their methodological limitations related to confounding by indication and selection bias\textsuperscript{72,98,104,195}. Adoption of this approach has been limited, and Hartmann’s procedure remains the most frequently utilized operative strategy in the emergency setting, with rates remaining relatively constant over the past
decade. Our findings are consistent with other population-based studies where minor or no reductions in rates of colostomy have been identified, and might be attributable to two factors: 1) patients requiring operative intervention now are more likely to have complicated and severe disease, increasing the risk of a failed primary anastomosis; 2) conventional teaching which dictates avoidance of a colorectal anastomosis in the setting of any intra-abdominal infection. While the former might be appropriate, the latter might be more amenable to change over time as further evidence accrues. It is plausible that Hartmann’s procedure may be the safest option for high-risk patients with hemodynamic instability or significant comorbidity, providing lower-risk patients the opportunity for a less morbid intervention. Further randomized trials are needed to compare primary anastomosis, with and without diverting ileostomy, to Hartmann’s procedure for patients with Hinchey III and IV diverticulitis. Future research should be aimed at determining the patient factors that predict high risk of failure of primary anastomosis to help guide patient selection. Additionally, reports suggest that surgeon factors may also be a predictor of the type of operation selected for acute complicated diverticulitis, with non-colorectal surgeons being more likely to perform Hartmann’s procedure despite similar patient factors and disease severity. Knowledge translation and standardization of best practices may help reduce the unnecessary use of Hartmann’s procedure for patients who can safely be treated with primary anastomosis.

6.4.2 Indications for elective colectomy following diverticulitis

The operative risks associated with elective colectomy must be considered in the decision to offer a patient resection of the diseased bowel segment following successful non-operative management of the acute episode. In the current study, the in-hospital mortality was low at 0.2%; prior reports have quoted mortality rates in the range of 0-4% and morbidity rates up to 22-
In this cohort, a significant proportion (7.5%) of patients undergoing elective surgery following diverticulitis received either an ileostomy or colostomy, other studies have reported this risk to be as high as 15%. Elective colon resection for diverticular disease has been observed to carry a greater morbidity and mortality than colon resection for cancer, with greater hospital costs and longer length of stay in hospital. Furthermore, elective colectomy does not guarantee prevention of disease recurrence, the risk of postoperative recurrence has been shown to range from 5.8% to 8.7%. Furthermore, up to 20-25% of patients may experience persistent abdominal symptoms after elective colon resection for diverticular disease. These data suggest that elective colectomy is associated with significant morbidity and risks, and does not prevent all disease recurrences.

Consistent with the above findings, we have observed a significant decline in the use of elective colectomy following successful non-operative management of diverticulitis. However, it remains unclear at present which patients truly benefit from elective colectomy following successful non-operative management. To determine which patients should be offered elective surgery, future research should aim to compare the risks and benefits of elective colectomy against conservative management for high risk patient subgroups, such as patients with multiple recurrent episodes, persistent abdominal symptoms, high risk medical comorbidities, and those with large, pelvic abscesses that have been successfully drained percutaneously. Results from randomized trials comparing elective surgery to non-operative management in reducing disease-related mortality, morbidity, quality of life, and healthcare costs will add new knowledge to better inform treatment decisions.
References


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107. Swank HA, Vermeulen J, Lange JF, et al. The ladies trial: laparoscopic peritoneal lavage or resection for purulent peritonitis and Hartmann's procedure or resection with primary anastomosis for purulent or faecal peritonitis in perforated diverticulitis (NTR2037). *BMC surgery* 2010; **10**: 29.


## Appendices

### Appendix 1: Relevant ICD-10-CA diagnosis and procedure codes

<table>
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<tr>
<th>Exclusion Criteria:</th>
<th>ICD code, OHIP Billing Code</th>
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<td>Gastro-intestinal bleeding</td>
<td>ICD-10 diagnosis codes: K55.2, K55.20, K558, K57.21, K57.33, K62.5, K921, K922</td>
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| Prior colon cancer | ICD-10 diagnosis codes: C18-C21, D12  
| Prior colorectal resection | ICD-9 procedure codes: 57.5x, 57.6x, 60.4x, 60.5x  
ICD-10 procedure codes: 1.NM.87x, 1.NM.89x, 1.NM.91x, 1.NQ.87x, 1.NQ.89x, 1.NQ.90x.  

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<td>Operative drainage of abdominal cavity/ abscess (open and laparoscopic)</td>
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<tr>
<td>Open drainage of rectal abscess</td>
<td>1.NQ.52.LA, 1.NQ.52.LATS</td>
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<tr>
<td>Diagnostic laparoscopy</td>
<td>2.OT.70.DA</td>
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<tr>
<td>Diagnostic laparotomy</td>
<td>2.OT.70.LA, 2.NM.70.LA</td>
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| Ileostomy | 1.NK.77.XX, 1NQ89LHXG, 1NQ89RSXXG  
1.NM.77.XX, 1NM87TF, 1NM87TG, 1NM89TF, 1NM91TF, 1NM91TG, 1NQ87TF, 1NQ89LH, 1NG89RS, |
| Colostomy | Repair large intestine | 1.NM.80.XX |
| Partial colectomy | 1.NM.87.XX |
| Partial excision of rectum | 1.NQ.87.XX |
| Total excision of rectum | 1.NQ.89.XX |
| Total excision of rectum with reconstruction | 1.NQ.90.XX |
| Total colectomy | 1.NM.89.XX |
| Radical excision of large intestine | 1.NM.91.XX |
| Closure of small or large bowel fistula | 1.NP.86.XX |
| Closure of rectal fistula | 1.NQ.80.XX |
| Laparoscopic or laparoscopic – assisted technique | 1NM76DF, 1NM76DN, 1NM80DA, 1NM80DAFH, 1NM80DAW2, 1NM80DAW3, 1NM80DAXXE, 1NM87DA, 1NM87DE, 1NM87DF, 1NM87DN, 1NM87PN, 1NM89DF, 1NM91DE, 1NM91DF, 1NM91DN, 1NQ87DA, 1NQ87DE, 1NQ87DF, 1NQ87PN, 1NQ87DF, 1NQ87DN, 1NQ87EP, 1NQ87DX, 1NQ87DY, 1NQ89AB |