Late Surgical Complications of Roux-en-Y Gastric Bypass

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Late surgical complications of Roux-en-Y gastric bypass

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The findings of the five original studies included in this thesis aid clinicians in their understanding and treatment of complications of Roux-en-Y gastric bypass surgery.

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Abstract

This thesis aims to investigate challenges in diagnosing and managing late surgical complications of Roux-en-Y gastric bypass (RYGB) experienced by acute care surgeons.

The advancement of bariatric surgery as a mainstay treatment for the obesity pandemic meant that Roux-en-Y gastric bypass became the most common bariatric procedure in Sweden during the past decade. This consequently brought a new category of patients to the emergency room with late complications. The most common late surgical complication of RYGB with a frequency of up to 16% in 10 years was internal herniation (IH), which could occur in the mesenteric gaps formed after the Roux-en-Y bypass. IH was notoriously difficult to diagnose, with patients presenting with varying clinical symptoms and without peritonitis, elevated laboratory tests, or disturbed vital signs making the clinical evaluation challenging. If a computed tomography report was also inconclusive, patients sometimes needed to undergo acute explorative surgeries. These surgeries were often negative without clear evidence of what caused the patient's severe discomfort. Bariatric surgeons learned to close the mesenteric gaps, which reduced the incidence of IH, but some risks remained and even patients treated for an IH had risk of recurrence. In Paper I, a retrospective cohort study, all RYGB-operated patients admitted to the surgical ward at Skåne University Hospital from April 2012 to June 2015 were included. The diagnosis and outcome of this cohort were published and IH was confirmed as the most common complication. Interestingly, half of the patients had unexplained abdominal pain. Paper II was a long-term follow-up study that showed an IH recurrence rate of 12% in 6 years and reiterated the importance of carefully examining both mesenteric gaps as all recurrences occurred at the untreated site. To evaluate the potential use of ischemia biomarkers citrulline, intestinal fatty acid binding protein, and D-dimer in diagnosing IH, Paper III was designed as a prospective study of all admitted RYGB patients with abdominal pain. The results of the study did not support the use of these ischemia biomarkers in diagnosing IH.

We shifted focus toward another RYGB-specific complication, namely intussusception. Jejunal intussusceptions can be asymptomatic but can also cause small bowel obstruction. In Paper IV, two radiologists reevaluated radiological findings of intussusceptions in RYGB patients and then compared them to the clinical outcome. The study found that the intussusception length on CT directly correlated to its risk of causing a small bowel obstruction needing surgery.

Finally, another difficulty arising as a result of the Roux-en-Y bypass is the management of common bile duct stones. As the duodenum has been bypassed, reaching the common bile duct endoscopically is difficult. Paper V, a national registry study, was used for a comparison between laparoscopic transcystic common bile duct exploration and intraoperative ERC for 2011-2020. The results showed that both methods were comparable, with few complications. In conclusion, this thesis has added valuable scientific knowledge to the field of late surgical complications of Roux-en-Y gastric bypass surgery, which can help surgeons in managing their patients.

Key words Gastric bypass, choledocholithiasis, internal hernia, intussusception, computed tomography, biomarkers.

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To my mom and dad
for always being proud of me
no matter the achievement

And to my wife
for always being by my side and
supporting me

And to my children Ismail and Alisha
as an inspiration to do greater

Table of Contents

Abstract

The aim of this thesis is to investigate challenges in diagnosing and managing late surgical complications of Roux-en-Y gastric bypass (RYGB) experienced by acute care surgeons.

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intussusceptions in RYGB patients and then compared them to the clinical outcome. The study found that the intussusception length on CT directly correlated to its risk of causing a small bowel obstruction needing surgery.

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Original papers

This doctoral thesis comprises the following original papers which are referred to in the text by their Roman numerals:

I. **Zaigham H**, Ekelund M, Regnér S, Olsson Å. Abdominal pain after gastric bypass in the acute general surgical care setting. Surg Obes Relat Dis. 2020; 16(12): 2058-2067.
doi:10.1016/j.soard.2020.07.008

II. **Zaigham H**, Ekelund M, Regnér S. Long-term follow-up and recurrence risk of internal herniation after Roux-en-Y gastric bypass. *Submitted manuscript.*

III. **Zaigham H**, Olsson Å, Ekelund M, Regnér S. The role of citrulline, intestinal fatty acid-binding protein, and D-dimer as potential biomarkers in the diagnosis of internal herniation after Roux-en-Y gastric bypass. Surg Obes Relat Dis. 2021;17(10):1704-1712.
doi:10.1016/j.soard.2021.05.028
Dan AG, Mellert LT. Comment on: The role of citrulline, intestinal-fatty acid binding protein and D-dimer as potential biomarkers in the diagnosis of internal herniation after Roux-en-Y gastric bypass. Surg Obes Relat Dis. 2021;17(10):1712-1713.
doi:10.1016/j.soard.2021.06.016

IV. **Zaigham H**, Ekelund M, Lee D, Ekberg O, Regnér S. Intussusception after Roux-en-Y gastric bypass: Correlation between radiological and operative findings. *Accepted manuscript.*

V. **Zaigham H**, Enochsson L, Ottosson J, Regnér S. Laparoscopic transcystic stone extraction vs. transgastric endoscopic retrograde cholangiography at cholecystectomy after Roux-en-Y gastric bypass. *Submitted manuscript.*

List of abbreviations

ASA = American society of anesthesiology

ASMBS = American Society for Metabolic and Bariatric Surgery

BMI = Body mass index

BPD-DS = Biliopancreatic diversion – duodenal switch

CBD = Common bile duct

CRP = C-reactive protein

CT = Computed tomography

CVD = Cardiovascular disease

ERC = Endoscopic retrograde cholangiography

ERCP = Endoscopic retrograde cholangiopancreatography

ER = Emergency room

ESG = Endoscopic sleeve gastrectomy

ICD = International statistical classification of diseases

I-FABP = Intestinal-type fatty acid-binding protein

IFSO = International Federation for the Surgery of Obesity and Metabolic Disorders

IH = Internal herniation

JJ = Jejuno-jejunostomy

LTCBDE = Laparoscopic transcystic common bile duct exploration

MRCP = Magnetic resonance cholangiopancreatography

NIH = National Institute of Health

NRS = Numeric rating scale

OAGB = One anastomosis gastric bypass

ρ = Probability

RYGB = Roux-en-Y gastric bypass

SADI = Single-anastomosis duodenal-ileal bypass

SBO = Small bowel obstruction

SOReg = Scandinavian Obesity Surgery Registry

tERC = transgastric endoscopic retrograde cholangiography

VBG = Vertical banded gastroplasty

WBC = White blood cell count

WHO = World Health Organization

Preface

As an acute care surgeon, in the early 2010s, I encountered a rising number of Roux-en-Y gastric bypass operated patients being admitted for acute abdominal pain. These patients represented a new, interesting, and challenging patient cohort that we had not experienced before. Some had serious complications, such as bowel perforation or bowel ischemia from internal herniation. Others seemed to have abdominal pain that we could not find a cause for. Radiologists needed to learn the altered anatomy and look for new radiological signs of internal herniation. They reported jejunal intussusceptions more often than ever before. Surgeons needed to learn to treat late surgical complications and had to perform an increasing number of explorative laparoscopies, as part of the investigation of acute abdominal pain. Many laparoscopies had unremarkable findings. Some patients suffered from chronic pain and were admitted multiple times, and each time it was equally challenging to rule out a serious complication. The Roux-en-Y anatomy also complicated the management of choledocholithiasis, and I felt the need to learn a new surgical technique to be able to manage these. I learned laparoscopic transcystic common bile duct exploration which had been successfully introduced to our Skåne University Hospital by Associate Professor Dr. Agneta Montgomery and Associate Professor Dr. Ulf Pettersson.

These new challenges were important to address. At that time, Dr. Åsa Olsson who also got intrigued by these challenges introduced me to a clinical research proposal. It was a research project concerning acute surgical care for gastric bypass patients. I immediately felt that it was a great opportunity for a Ph.D.-project. My main supervisor Associate Professor Dr. Sara Regnér helped formulate a Ph.D. project and has guided me ever since. Dr. Olsson became my co-supervisor and had already begun to include patients prospectively when I joined the project in 2013. Associate Professor Dr. Mikael Ekelund served as our bariatric surgery expert and his subject expertise was greatly appreciated when dealing with post-RYGB patients. He also accepted to become my co-supervisor. With the help of our wonderful "Acute Surgical" team in Malmö, we shifted focus in 2015 to our prospective study of investigating potential biomarkers to aid in the diagnosis of internal herniation. All colleagues helped out by including patients to the study. I later planned for a radiological study together with Professor Dr. Olle Ekberg. Collecting a prospective cohort took time, and since we had several

years of follow-up data, I was able to also design a long-term study to investigate the recurrence rate and treatment of the patients that had been treated for an internal herniation in our first retrospective cohort.

I feel blessed, proud, and humble for all the support that has finally led me to complete my thesis. I hope that my research efforts will be read with interest by acute care surgeons, general surgeons, bariatric surgeons, gastroenterologists, nurses, and other hospital staff, the general public interested in bariatric surgery, and the greater community so that it may help as many as possible to improve understanding and healthcare for Roux-en-Y gastric bypass operated patients.

Introduction

Obesity is defined by the WHO (World Health Organization) as "*abnormal or excessive fat accumulation that may impair health*". WHO considers Body Mass Index (BMI) to be the most useful population-level measure of overweight and obesity, "*as it is the same for both sexes and for all ages of adults*". BMI is defined as a person's weight in kilograms divided by the square of his height in meters (kg/m^2). A person with a BMI of ≥25 is defined as overweight, while one with a BMI ≥30 is defined as obese. Other measures of obesity have been proposed, such as waist circumference, or waist-to-hip ratio in an attempt to better measure the more harmful visceral adiposity. However, so far, BMI remains the universal definition despite its apparent limitations.

History of bariatric surgery

The first reported abdominal surgery for weight loss was in 1952. It was performed on an obese 32-year-old woman by Swedish surgeon Viktor Henriksson.[1] He had previously made observations that small bowel resections could result in weight loss, so he chose to resect 105 cm of the small bowel. This resulted in little weight loss, but he registered an improvement in the patient experienced quality of life. The idea of an irreversible surgical procedure did not catch on, however, in 1953, Dr. Varco at the University of Minnesota performed the first jejunoileal bypass surgery for weight-loss purposes. This operation was primarily focused on treating dyslipidemia and was planned to be reversible.[2] Dr. Kremen and coworkers, also from the University of Minnesota, studied small bowel bypasses on dogs and published the first series in 1954 showing that bypassing >50% of small bowel resulted in weight loss.[3] Variants of the jejunoileal bypass procedure were performed in the 1960s and early 1970s. These were initially planned as reversible procedures, however, results showed severe weight rebound after reversal. More than 30.000 such procedures were reported to have been performed despite serious complications and a mortality rate of up to 10%![4] The complications included severe diarrheas with electrolyte disturbances, nutritional deficits resulting in anemia, night blindness (vitamin A deficiency), osteomalacia (vitamin D deficiency), kidney stones, and severe liver disease (protein deficiency). These procedures were not received well by surgeons, perhaps rightly, and were eventually abandoned.[4]

In this context, we must remind ourselves that doctors take the Hippocratic oath in which one of the main promises is "*primum non nocere*", i.e. first, do no harm. To perform surgery with the sole purpose of weight loss requires that obesity be considered a disease and that no better treatment is available to the patient. It may easily be assumed that obesity could be treated by means of a diet with calorie restriction, exercise programs, coaching or therapy, or by pharmaceutical means. All of which have little or few side effects. Over the years, however, an increasing body of evidence has shown that bariatric surgery, or metabolic surgery as some prefer to call it, is safe and has longer-lasting effects, while most other means of weight loss have high rebound rates.

Gastric bypass

A major milestone occurred in 1967 when Dr. Mason developed the first gastric bypass procedure.[5] He hypothesized that limiting intake, instead of relying on malabsorption, may be a better approach to achieving weight loss.[6] His team had noted that total or sub-total gastrectomies for ulcer disease often resulted in significant weight loss. After performing gastroenterostomy experiments on dogs, they concluded that a subtotal gastric bypass would be suitable for obese patients.[7] The procedure was similar to the already familiar Billroth-II surgery, and therefore surgeons were comfortable adopting the new procedure which quickly gained popularity. Comparative studies of the new procedure to the earlier jejunoileal bypass showed favorable results. Mason's early gastric bypass, however, was plagued by biliary reflux because of the small bowel loop. This pushed the development of the Roux-en-Y type anastomosis in 1977. The technique was further developed in the 80s and 90s along with experiments with a multitude of other surgical procedures.

Undoubtedly the greatest breakthrough came with the introduction of minimally invasive surgery. In 1994, Wittgrove et al. published reports of the first five laparoscopic gastric bypass surgeries, describing the procedure in detail (Figure 1-4 with permission, Copyright © 1994, Springer).[8] Remarkably, these patients were all discharged on postoperative day two despite the long and technically difficult surgeries at the time. Two years later, in 1996, the first Swedish paper on laparoscopic gastric bypass was published by Lönroth et al.[9] Laparoscopic Roux-en-Y gastric bypass has since been developed and established itself as the Gold Standard for bariatric procedures, significantly reducing perioperative morbidity and mortality.[10-13] In 1998, American actress and celebrity Roseanne Barr publicly announced that she had undergone a gastric bypass procedure and visibly lost almost 50 kilos. Other celebrities followed and popularity grew to the extent that by 2011 it was estimated that 340.000 gastric bypass surgeries had been performed worldwide.[14]

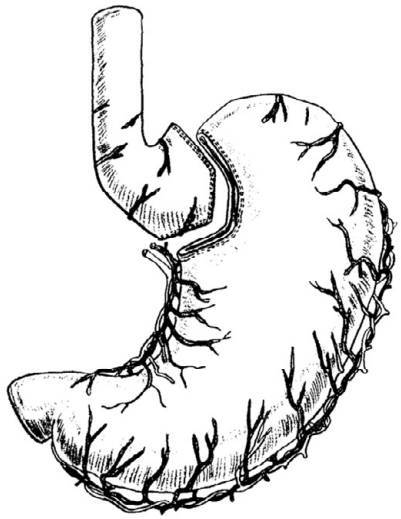


Figure 1. The stomach is transected with a series of applications of the endoscopic linear cutter, forming a curvilinear staple line.

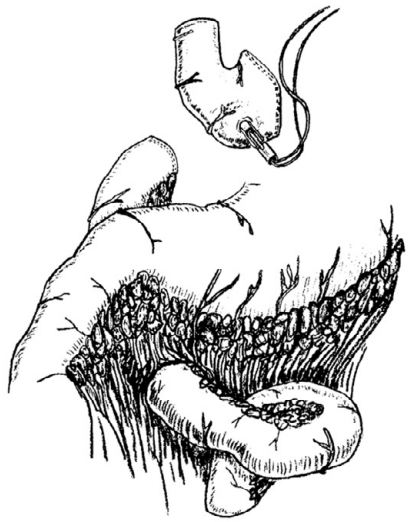


Figure 2. After insertion of the Stealth anvil per-orally, the proximal end of the Roux-limb is passed behind colon and stomach, to emerge from the upper recess of

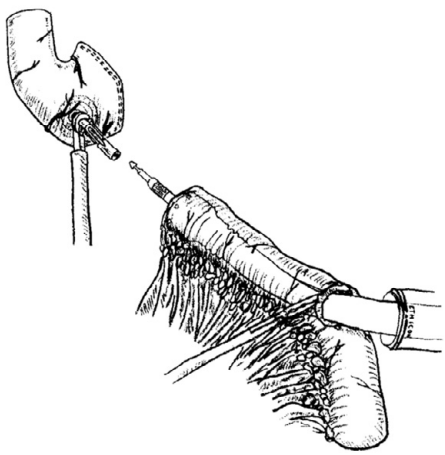


Figure 3. The Stealth is inserted through a counter-incision in the Roux-limb, and the penetrator is extended and is united with the stem of the anvil.

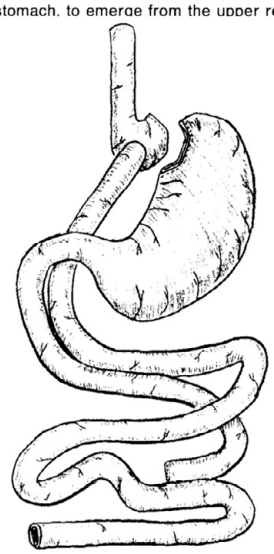


Figure 4. Completed anatomy is entirely similar to usual Roux-en-Y gastric bypass. Pouch is approximately 30 cc, and diameter of gastroenterostomy stoma approximately 12 mm.

Other bariatric surgeries

Meanwhile, other surgeries were developed with varying success. Bariatric surgeries were commonly divided into two categories, restrictive or malabsorptive (also called hypoabsorptive). The gastric bypass is somewhere in between, but mainly a restrictive procedure, because of the small gastric pouch. The chosen size of the gastric pouch became gradually smaller over time, as studies showed that larger pouch sizes increased the risk of dilatation over time with weight regain and had an increased risk of marginal ulcers (stomal ulcers) in the gastrojejunostomy.[15-16] As the gastric bypass procedure was technically complicated, simpler procedures were invented, particularly of the restrictive type. Dr. Wilkinson et al. first proposed a restrictive "Nissen-type" gastric wrap procedure to reduce gastric intake.[17] The broader introduction of the stapler instrument in the 1970s, meant that new procedures could be developed.[18-19] Several variants of the vertical banded gastroplasty (VBG) were developed to simply create a small gastric pouch to reduce intake.[20] This procedure was simplified by the introduction of gastric banding, which used a vascular graft to create a narrow ring around the fundus. [21-22] Although the technique was simpler, results varied as standardization was difficult when one size did not fit all. Surgeons were looking for an adjustable alternative to the band which was eventually developed simultaneously by Dr. Hallberg in Sweden and Dr. Kuzmak in the United States.[23-25] These procedures also benefited from the introduction of minimally invasive surgery.[26-27] The laparoscopic gastric band became the most popular bariatric surgery in Europe and the United States.[4] Although it was a fast and easy procedure with low morbidity it was eventually almost abandoned due to weight regain and long-term complications, such as band slippage, erosion, and foreign body infection.

Some surgeons instead contended that malabsorption was needed for long-term weight loss. Biliopancreatic diversions were developed with the Duodenal Switch, reported by Marceau and Hess, becoming most accepted.[28-29] These surgeries were complex consisting of a vertical gastrectomy (sleeve) and an ileal bypass, i.e. duodenal switch. Because of its complexity, the procedure was later suggested to be staged into two parts.[30] It was then revealed that the safer sleeve gastrectomy, i.e. the first stage, by itself showed substantial weight loss. Many patients opted out of the second stage of ileal bypass surgery appreciating an adequate weight loss from the sleeve gastrectomy paving the way for it to become a stand-alone procedure in its own right. Over time sleeve gastrectomy has become the most popular bariatric operation worldwide.

In more recent years, further development of these procedures has taken place. The Single Anastomosis Duodenal-Ileal bypass with sleeve (SADI-S) was a malabsorptive technique developed in 2007 as an alternative to biliopancreatic diversions or as a revision to a failed sleeve gastrectomy.[31-32] It consists of a sleeve gastrectomy with the

stapled division of the proximal duodenum. An antecolic and isoperistaltic duodenoileal anastomosis is constructed to a loop of bowel 250-300 cm proximal to the ileocecal junction. It is regarded as an option for the morbidly obese or after failed sleeve gastrectomies.

The Roux-en-Y gastric bypass procedure was also further developed by simplifying it to a one-anastomosis gastric bypass (OAGB).[33] First, a stapled long pouch along the lesser curvature is constructed and then an omega loop of bowel 200 cm distal to the ligament of Treitz is anastomosed to the gastric pouch. Although it was reported as the third most common bariatric procedure worldwide, numerous areas of non-consensus remain in its use and technique. This procedure is also called single anastomosis gastric bypass, mini gastric bypass, or omega loop gastric bypass and it has similar or better weight loss compared to Roux-en-Y gastric bypass.[34] This technique, however, has a higher degree of malabsorption and, as a consequence, an increased frequency of malnutrition compared to Roux-en-Y gastric bypass. OAGB is therefore reserved for the morbidly obese. Another drawback is the varying degree of bile reflux which may trigger the need for revisional surgery with an enteroanastomosis to deviate the bile fluid.

In recent years, the improvement of endoscopic technique and the advent of endoscopic suturing devices, such as the OverStitch™ endoscopic suturing system (Apollo Endosurgery, Austin, Texas), has enabled endoscopists to enter the field of bariatric procedures.[35] Currently, endoscopic sleeve gastroplasty is being evaluated as a cheaper and reversible alternative to sleeve gastrectomy (Figure 5), however, the remaining blind gastric mucosa is a subject of uncertainty for fear of future malignancy.[36] Other applications include use for revisional surgery, e.g. after Roux-en-Y gastric bypass, where a dilated gastric pouch or gastrojejunostomy is treated endoscopically. [37] Another use is as a revision after sleeve gastrectomy where endoscopic suturing may be used to narrow the gastric tube. [38]

Notably, during the development of bariatric procedures, it became apparent that, aside from weight loss, numerous comorbidities were alleviated. Perhaps most importantly, diabetes resolved or improved substantially for a multitude of patients.[39] Consequently, surgery was soon being discussed as a treatment option for diabetes or that surgery at least should be considered for lower BMI thresholds in patients with diabetes. This was further discussed in 1978 by Richard L. Varco and Henry Buchwald in their book "Metabolic Surgery", which they defined "*as the operative manipulation of a normal organ or organ system to achieve a biological result for a potential health gain*".[40] Thereby shifting focus to the metabolic effects of the bariatric procedure aside from the apparent weight loss.

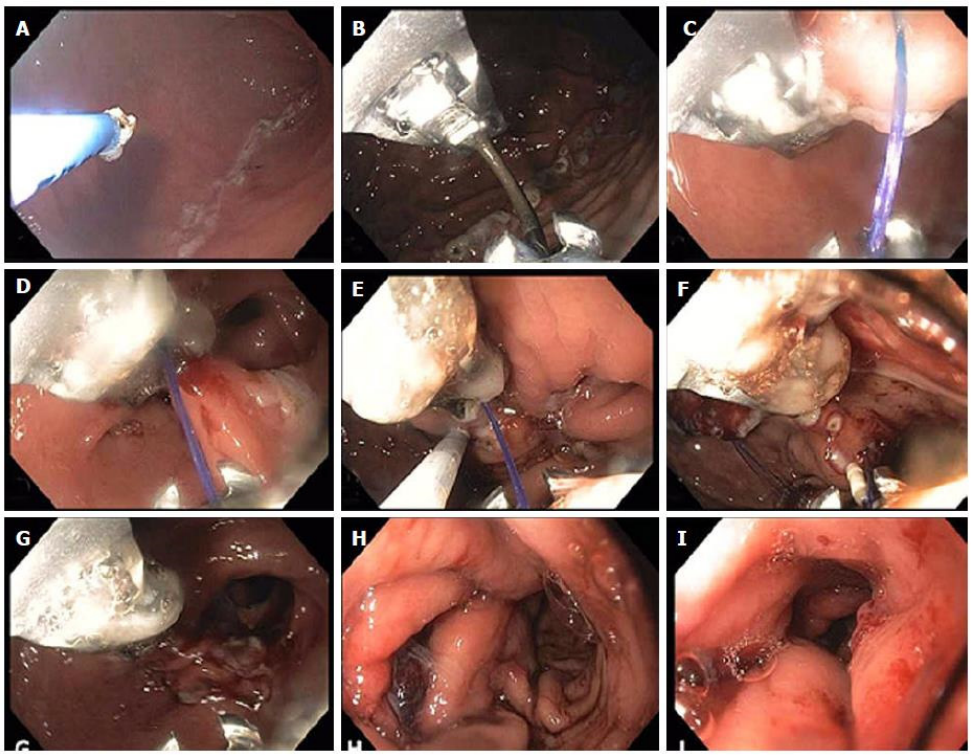


Figure 5. Endoscopic sleeve gastroplasty, up and coming? (Copyright © Stavropoulos et al. 2015, Extracted from Stavropoulos SN, Modayil R, Friedel D. Current applications of endoscopic suturing. World J Gastrointest Endosc 2015; 7(8): 777-789 [PMID: 26191342, doi: 10.4253/wjge.v7.i8.777])

Through continued improvements and closely monitored follow-up, the procedures kept improving, thereby lowering morbidity and mortality over the years. The Swedish SOS study played an important role in providing evidence of the value of bariatric surgery.[41] This was a prospective controlled trial of 4047 obese patients. In total 2010 patients in the surgical group underwent bariatric surgery including gastric bypass, gastric banding, and vertical banded gastroplasty, whilst 2037 patients were in a matched control group undergoing conventional treatment. Patients were followed for 14.7 years (median). The results showed that surgery, compared to conventional treatment, was associated with a long-term reduction in overall mortality and decreased incidence of diabetes, myocardial infarction, stroke, and cancer.[42-45] These results were confirmed by numerous other studies at a time when quality assessment and monitoring in healthcare became increasingly important.

Obesity epidemic

Obesity was recognized as a major public health problem and a global epidemic by the WHO in 1997.[46] The National Institute of Health (NIH) declared obesity a disease in 1998 when publishing a comprehensive 262-page report with clinical guidelines for the treatment of overweight and obesity.[47] This was in collaboration with the National Heart, Lung, and Blood Institute (NHLBI) and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), signifying the metabolic multifactorial nature of obesity. At that time, they estimated that 97 million adults in the United States were overweight or obese and that "*the total costs of obesity-related disease approached $100 billion annually*".[47] They also issued an evidence statement and recommendation in support of surgical intervention and mentioned the two techniques available at the time, vertical gastric banding and Roux-en-Y gastric bypass.

> **Evidence Statement:** Gastrointestinal surgery (gastric restriction [vertical gastric banding] or gastric bypass [Roux-en Y]) can result in substantial weight loss, and therefore is an available weight loss option for well-informed and motivated patients with a BMI ≥ 40 or ≥ 35, who have comorbid conditions and acceptable operative risks. Evidence Category B.[37]

The decision to recognize obesity as a disease was still controversial at the time and it was not until June 2013 that the American Medical Association (AMA) would do the same. They then announced that: "*Our AMA recognizes obesity as a disease state with multiple pathophysiological aspects requiring a range of interventions to advance obesity treatment and prevention*".[48]

Obesity has since been recognized as a growing public health problem worldwide. A comprehensive study published in the Lancet in 2016, reported a tenfold increase in childhood and adolescent obesity in four decades.[49] Geographical distributions of mean BMI, overweight and underweight boys and girls are shown in Figure 6. The latest report from the WHO in 2016 stated that 1.9 billion adults (39%), 18 years and older, were overweight. Of those, over 650 million adults (13%) were obese.[50] They further reported that these numbers had tripled since 1975 and that more people now died of being overweight or obese than of being underweight. In the United States, the National Center for Health Statistics published a National Health and Nutrition Examination Survey (2017–March 2020 pre-pandemic data files) in 2021 that estimated a national obesity prevalence of 41.9% in adults aged 20 years and over.[51] The Public Health Agency of Sweden (Swedish: Folkhälsomyndigheten) reported 16% obesity and 36% overweight in individuals aged 18-84 years in its latest report for 2021.[52]

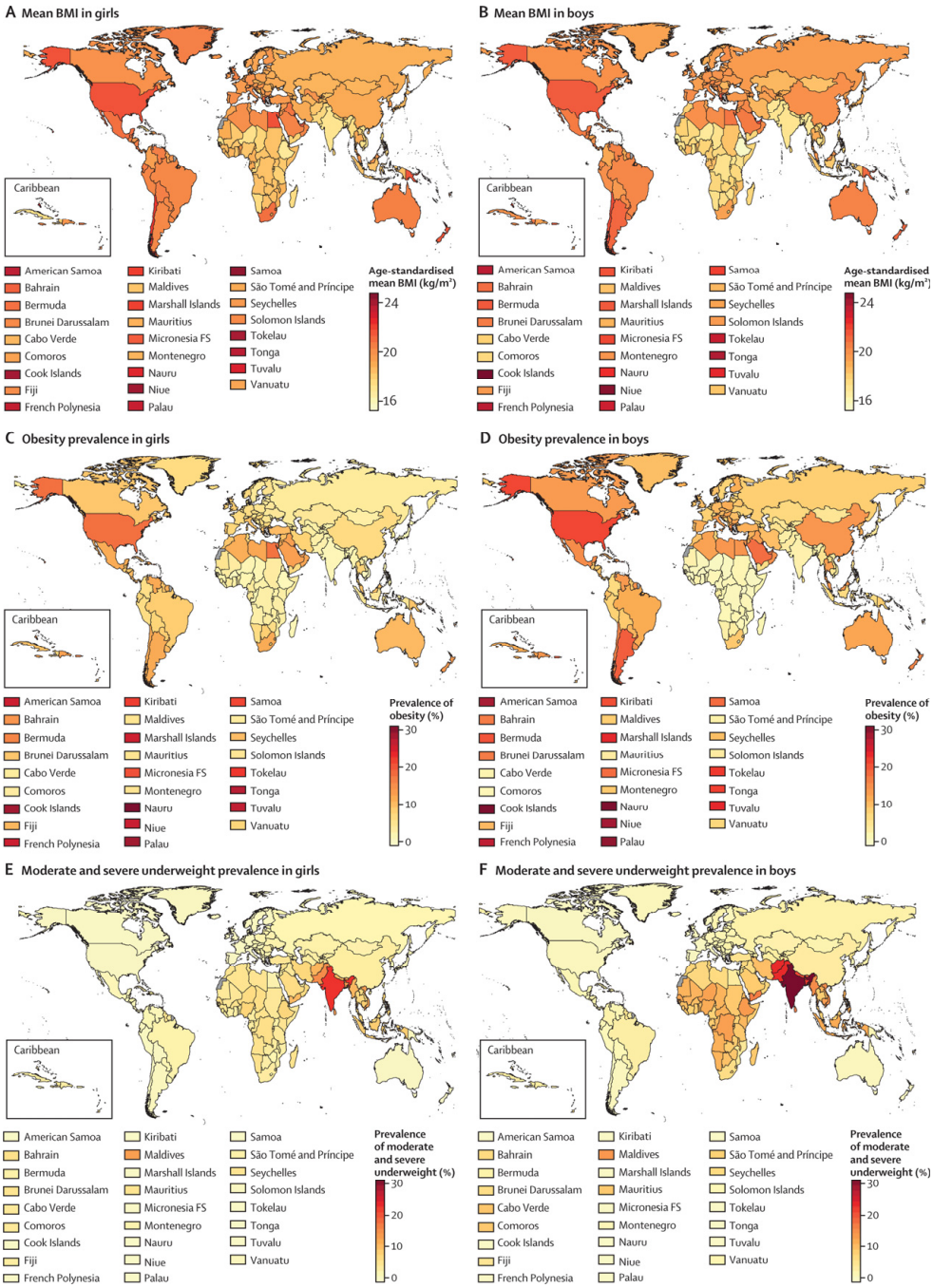


Figure 6. Reproduced with permission from "Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128·9 million children, adolescents, and adults." Lancet. 2017;390(10113):2627-2642. doi:10.1016/S0140-6736(17)32129-3

National registries

At a time when bariatric surgery was growing worldwide, its popularity in Sweden also grew. To ensure quality control, the Scandinavian Obesity Surgery Registry (SOReg) began recording perioperative data for bariatric surgeries in May 2007.[53] SOReg, now one of more than 100 national quality registries, quickly reached an impressive coverage rate and has been repeatedly validated with excellent results.[54-55]

Another register used in this thesis was GallRiks—The Swedish Registry of Gallstone Surgery and Endoscopic Retrograde Cholangiopancreatography (ERCP), which was launched in May 2005.[56] GallRiks was developed for the purpose of quality assurance and research and is endorsed by the Swedish Surgical Society. Cholecystectomies, as well as all endoscopic interventions of the bile ducts, are included with an aim to achieve complete national coverage for the treatment of gallstones and their complications. It is also the world's first nationwide, web-based, quality registry for gallstone surgery and ERCP.[57] Swedish quality registries receive funding from the National Board of Health and Welfare (Swedish: Socialstyrelsen). In their annual coverage report for 2020, GallRiks reported a national coverage of 89.9% for ERCPs and 92.4% for cholecystectomies. SOReg reported a national coverage of 95.9% for bariatric surgeries.[58] Data from both registries have been used in numerous scientific publications.

Bariatric surgery in Sweden

For the years preceding the inception of the registry, SOReg used national patient registries to calculate the number of bariatric procedures (Figure 7).[59] The sharp increase seen in the 2010s was explained by the popularity of the laparoscopic gastric bypass procedure, which accounted for more than 95% of all bariatric procedures at the time (Figure 8).[59] In 2011, over 8000 surgeries were performed for a population of less than 10 million. These numbers have since slowly declined with a sudden dip during the COVID-19 pandemic in 2020. However, some concerns about the long-term complications of the RYGB procedure and the gaining popularity of sleeve gastrectomy, explain the current fifty-fifty balance between the two surgeries. For reference, the estimated number of bariatric surgeries in the United States for the past decade was added (Table 1).[60]

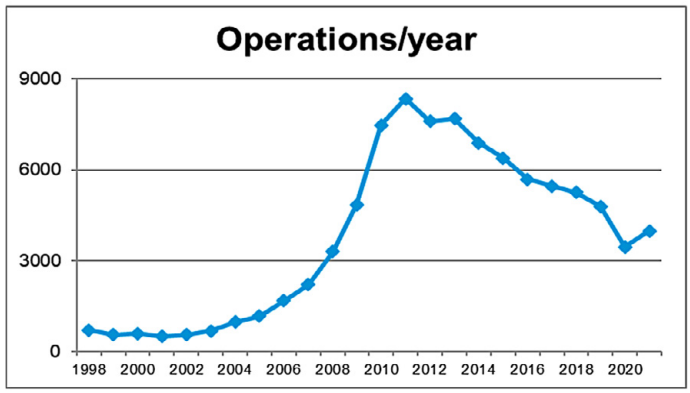


Figure 7. The number of bariatric surgeries in Sweden between 1998 and 2021 (Extracted with permission, SOReg Annual Report 2021-part 1 © 2022 SOReg).[59]

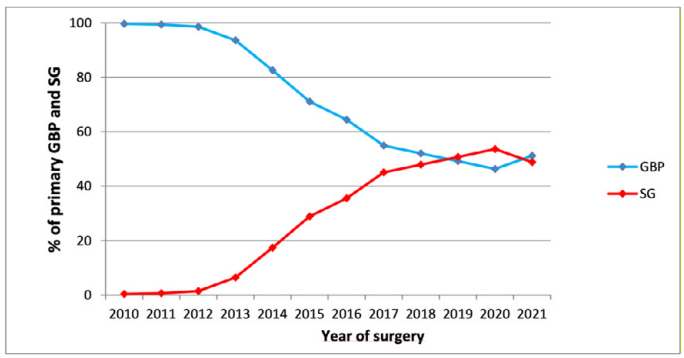


Figure 8. Distribution of bariatric surgeries showing distribution between gastric bypass (GBP) and sleeve gastrectomy (SG) from 2010 to 2021. (Extracted with permission, SOReg Annual Report 2021-part 1 © 2022 SOReg).[59]

Access to bariatric surgery across Sweden varies, as shown in Figure 9. The number of bariatric procedures in the region of Scania (Swedish: Skåne län), where the studies in this thesis were performed, was consistently above the country average (Swedish: Riket).[59] Each region in Sweden is a separate healthcare provider and has its own guidelines for bariatric surgery. The current obesity management guidelines for the region of Scania (Skåne) recommend bariatric surgery RYGB for adult patients with a BMI ≥40kg/m^2 or patients with an obesity-related comorbidity and a BMI ≥35 kg/m^2.

Interestingly, International Diabetes Organizations released a joint statement in 2016 in favor of metabolic surgery for diabetes. They recommended surgery for all diabetics with BMI ≥40 kg/m^2, for uncontrolled diabetes with BMI ≥35 kg/m^2, and stated that surgery can be considered for uncontrolled diabetes for BMI ≥30 kg/m^2.[62]

The national policy guidelines, *"Nationella riktlinjer för vård vid obesitas - Stöd för styrning och ledning 2022"* published by the National Board of Health and Welfare (Swedish: Socialstyrelsen), rank the priority of interventions from 1-10 (1=most important, 10=least important). The latest recommendations for bariatric surgery are more liberal than regional guidelines and recommend RYGB surgery for adult patients with a BMI ≥30kg/m^2 and 15-17-year-olds with a BMI ≥35 kg/m^2, with a priority three recommendation. A higher priority of two was given to the recommendation of RYGB surgery for adults with a BMI ≥35 kg/m^2. The guidelines further recommend gastric sleeve surgery for adult patients with BMI ≥35 kg/m^2 with a category three priority. [61] Duodenal switch is mentioned as an option for adults with BMI ≥50 kg/m^2, but only with a level five priority, after considering either RYGB or gastric sleeve surgery first. It is noteworthy that these guidelines do not weigh diabetes or any other comorbidity in their recommendations for bariatric (metabolic) surgery.

Laparoscopic gastric bypass surgery has become the mainstay bariatric surgery in Sweden and is performed with limited morbidity and mortality. It is the long-term complications, however, that have raised the greatest concern and are the topic of this thesis.

Table 1. Estimate of bariatric surgery numbers for the United States. [60]

	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
Sleeve	28,124	57,090	75,359	99,781	105,448	125,318	135,401	154,976	152,413	122,056
RYGB	57,986	64,875	61,218	51,724	45,276	40,316	40,574	42,945	45,744	41,280
Band	55,932	34,946	25,060	18,335	11,172	7,310	6,318	2,660	2,375	2,393
BPD-DS	1,422	1,730	1,790	772	1,176	1,236	1,588	2,123	2,272	3,555
Revision	9,480	10,380	10,740	22,195	26,656	30,077	32,238	38,971	42,881	22,022
SADI	—	—	—	—	—	—	—	—	—	488
OAGB	—	—	—	—	—	—	—	—	—	1,338
Other	5,056	3,979	4,833	193	6,272	5,665	5,606	5,847	6,060	1,221
ESG	—	—	—	—	—	—	—	—	—	1,500
Balloons	—	—	—	—	700	5,744	6,280	5,042	4,655	2,800
Total	158,000	173,000	179,000	193,000	196,700	215,666	228,005	252,564	256,000	198,651

Published June 2022, Accessed Sept. 27th 2022

ASMBS = American Society for Metabolic and Bariatric Surgery, RYGB = Roux-en-Y gastric bypass, BPD-DS = Biliopancreatic diversion – duodenal switch, SADI = Single-anastomosis duodenal-ileal bypass, OAGB = One anastomosis gastric bypass, ESG = Endoscopic sleeve gastrectomy.

The ASMBS total bariatric procedure numbers are based on the best estimation from available data (BOLD,ACS/MBSAQIP, National Inpatient Sample Data, and outpatient estimations). Republished with permission © 2022 ASMBS. All rights reserved. https://asmbs.org/resources/estimate-of-bariatric-surgery-numbers

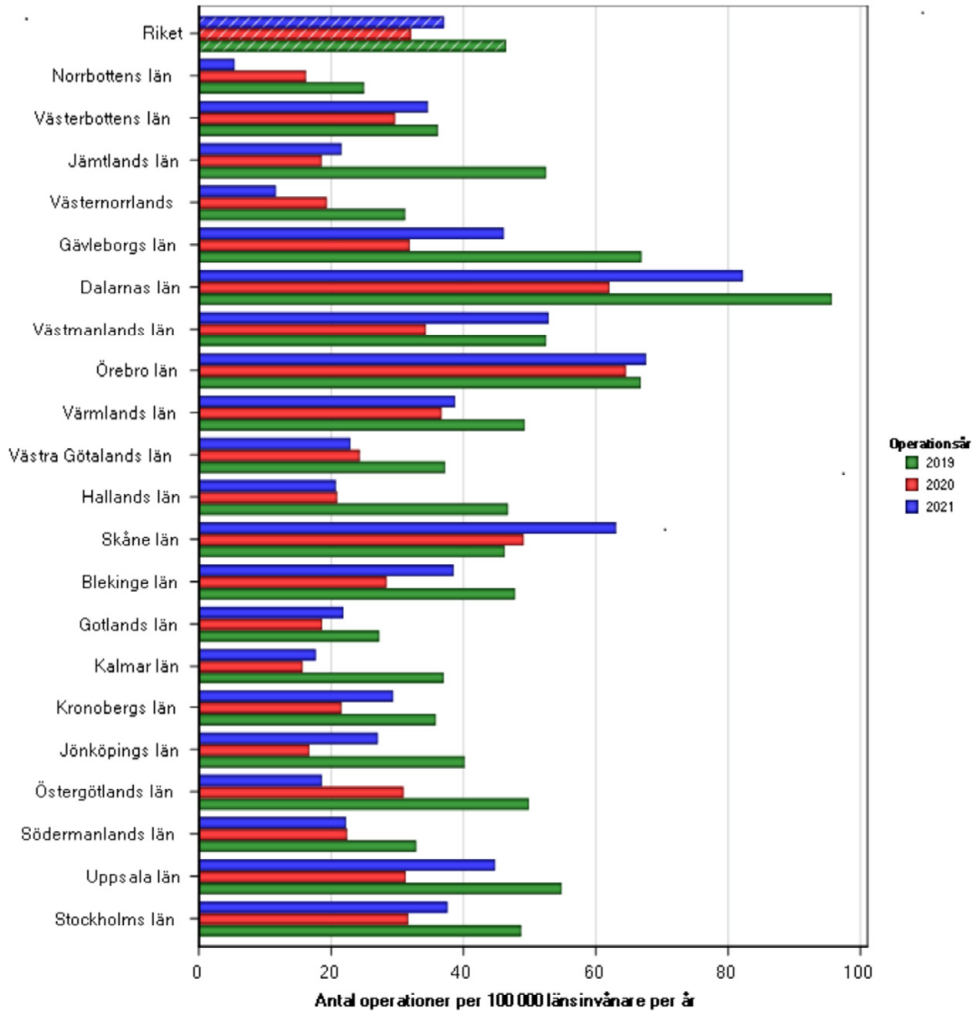


Figure 9. The number of bariatric surgeries per 100.000 inhabitants per region (Swedish:län) in Sweden compared to country average (Swedish: Riket) for 2019 to 2021 (Extracted with permission from SOReg Annual Report 2021-part 1 © 2022 SOReg).59

Surgical complications of Roux-en-Y gastric bypass

Early and late complications are defined as occurring within (≤30 days) or after 30 days, respectively. Although inherently different complications occur early or late, some late complications may occur within the first 30 days.

Early complications

Early surgical complications are typically anastomotic leaks, bleeding, bowel obstruction, and postoperative infections. While an anastomotic leak presents early with tachycardia and peritonitis, small bowel obstruction can occur at any time after surgery with varying causes. The incidence rate of anastomotic leaks reported in the literature is between 1.1% and 5.6%.[63-65] In Sweden, SOReg reported an anastomotic leak rate of 0.7% for 2021.[59] Anastomotic leaks usually require urgent operative suture repair with an omental patch, while stable patients may be treated conservatively. Lately, endoscopic stenting techniques have also shown promising results.[66-67]

The incidence rate of postoperative bleeding is between 1% and 4.1% in the literature.[68-71] Similarly, SOReg reported a postoperative bleeding incidence rate of 1.3% for 2021.[59] Postoperative bleedings are a cause of significant morbidity and usually present as melena and are most often due to staple-line bleeds. Though usually self-limited, it may require reoperation and is also associated with higher rates of additional postoperative complications.[71]

Early postoperative obstructions are rare and are associated with strictures or kinks in or near the gastrojejunostomy or jejunojejunostomy. An increased incidence of postoperative obstructions was seen after the introduction of routine closure of the mesenteric gaps.[72] SOReg reported a rate of around 1% for the past few years, with a North-Western European pooled multinational registry study citing 0.8%. [59,73]

Late complications

Late or long-term complications were rare in the emergency department prior to the historic rise in the number of bariatric procedures in the early 2010s. With an increasing number of patients having undergone bariatric surgery, which at the time was almost exclusively Roux-en-Y gastric bypass surgery, the number of patients seen at the emergency department successively increased. The main complaint was acute abdominal pain. These patients posed a particular challenge to acute care surgeons who had little or no prior experience with bariatric surgery. Some patients presented with unbearable pain that necessitated emergency surgery for fear of intestinal ischemia.

These patients rarely had peritonitis, affected vital signs, or raised lab tests to aid in the diagnosis and had to undergo emergency surgery by (at the time) inexperienced acute care surgeons who were unfamiliar with the bariatric procedure performed. Some patients were indeed suffering from bowel ischemia following internal herniations, while others did not seem to have any objective pathology. Eventually, attempts were made by both acute care surgeons and gastroenterologists to summarize the evaluation and management of common bariatric emergencies with a particular focus on Roux-en-Y gastric bypass operated patients.[74-76] The latest comprehensive guidelines on operative management of acute abdomen after bariatric surgery was published in 2022 by De Simone et al.[77]

Internal herniation

Internal herniation (IH) is defined as the protrusion of abdominal viscera through a peritoneal or mesenteric opening in the abdomen or pelvis. Internal herniations are rare in the healthy adult population and are most commonly caused by small bowels being trapped in mesenteric gaps or congenital defects. As congenital mesenteric openings are rare, they occur more commonly after intestinal surgery when the mesentery has been divided. Internal herniations differ from abdominal wall hernias in the sense that no protrusion is noticed through the abdominal wall and diagnosis is therefore difficult and sometimes delayed. Reliable diagnostic imaging is especially important, as well as maintaining a low threshold for surgical exploration.

Roux-en-Y gastric bypass surgery forms two mesenteric defects as a result of the Roux-en-Y reconstruction, one between the Roux (alimentary) limb and the transverse colon mesenteries, and the other between the jejunal mesenteries beneath the jejuno-jejunostomy (Figure 10). The earlier open procedure was retrogastric and retrocolic, i.e. placed the Roux-limb through the transverse mesocolon, the lesser sac, and behind the stomach and hence also formed a third defect through the transverse mesocolon that was susceptible to an internal herniation. The mesenteric defect between the alimentary limb and transverse colon mesenteries was first described by German surgeon Walther Petersen in 1900, and has thereafter been referred to as Petersen's space.[78] The most common laparoscopic technique in Sweden uses the antecolic, antegastric technique for the Roux-limb and hence has two sites susceptible to internal herniations, as described in a paper by Leifsson et al.[79]

In the shift toward the laparoscopic antecolic and antegastric approach, the mesenteric gaps were generally left without closure. It soon became apparent though that IHs were the most common, long-term complication of RYGB surgery. In long-term follow-up studies, incidence rates of up to 16% have been published.[80-82]

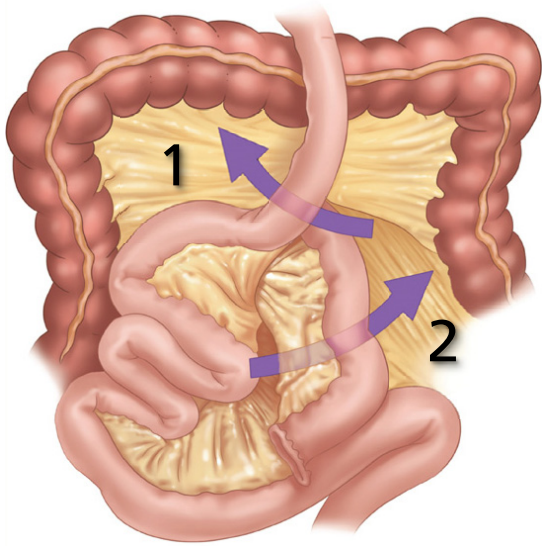


Figure 10. Arrows indicate sites for internal herniation after RYGB: (1) Petersen's space, between the Roux limb and the transverse mesocolon mesenteries; (2) the mesenteric defect beneath the jejuno-jejunostomy. (Reproduced with permission from Bariatric Times © Accessed Oct 5th, 2022).

Closure of mesenteric gaps

Focus quickly shifted toward interventions to reduce the unacceptably high incidence rates of IH. A randomized controlled trial by Stenberg et al. in 2012, comparing the outcome of closure vs. non-closure of the mesenteric gaps, received much due credit.[72] A shift toward closure of the mesenteric gaps began and soon a national expert group published evidence-based recommendations for routine closure of the mesenteric gaps at RYGB surgery.[83] Gradually it became common practice to check and close the mesenteric gaps during any laparoscopy for these patients. Soon, follow-up studies would verify the reduction of the incidence of internal herniations.[81,84-87]

The primary closure of the mesenteric gaps was performed using either clips or sutures, with small differences in the results.[89] A commonly used technique by bariatric surgeons in our region, is closure with Endo Hernia™ clips (Medtronic, Minneapolis, MN, USA), as described by Aghajani et al.[88] The shift to routine closure of the mesenteric gaps did not come without a price, as surgeons experienced an increased incidence of early bowel obstruction caused by kinks in the enteroanastomosis.[72,81,90-91] This complication, however, seemed to have a learning-curve effect, as the incidence has reduced over time with slight modification to the closure technique.[81,92]

Closure of the mesenteric gaps significantly lowered but did not eliminate the risk of internal herniation, since the closed mesenteric gaps could still reopen.[81,93] A Danish

group, Danshøj et al., reported a high recurrence rate of about 19% after surgery for internal herniation and showed that the risk of recurrence remained high even after secondary and tertiary closures.[94] They briefly discussed that this may be due to difficulty in identifying and closing the mesenteric defects correctly, and that a lack of experienced bariatric surgeons may influence the results. However, their data did not allow for determining the competency of the surgeon.

Diagnosis

Improving the diagnosis of internal herniation has been a focus of recent research efforts. Due to the great variance in clinical signs and a lack of laboratory tests, there is added importance to the role of imaging in diagnosing the condition. As computed tomography has become an integral part of evaluating acute abdominal pain in RYGB patients, radiologists have continuously improved the detection rate of internal herniation. New radiological signs and findings have been introduced over the years. The most well-known sign is the mesenteric "swirl sign" or "whirlpool sign" (Figure 11), whilst compression of the superior mesenteric vein was reported later.[95] There are now about ten radiological signs of internal herniations and the sheer number by itself illustrates the diagnostic challenge.[96-98] Despite the diagnostic challenges, it is now universally accepted that an abdominal computed tomography scan is reliable in diagnosing internal herniation in RYGB patients.[99]

Biomarkers

As mentioned above, the role of routine laboratory tests is limited in the diagnosis of internal herniation. Very few research studies have looked into the potential of diagnosing internal herniation using biomarkers. Case reports have consistently reported that internal herniations have occurred despite normal routine laboratory results, which has been confirmed by clinical experience. Studies have therefore continued to stress the importance of having a high level of clinical suspicion and a low threshold for surgical exploration.

In identifying a potential biomarker we must ask, what biochemical changes can be expected from an incarcerated bowel in an internal herniation? Since incarceration can eventually lead to bowel ischemia and necrosis, it would be reasonable to assume that ischemic biochemical changes occur. In fact, there has been extensive research on trying to find useful biomarkers for early diagnosis of acute mesenteric ischemia.[100-107] Studies have focused on acute mesenteric ischemia caused by both acute arterial occlusive disease and venous thrombosis. Some progress has been made, but the results have been conflicting and the diagnostic accuracy has been low. Some of the biomarkers that have been investigated for acute mesenteric ischemia include intestinal fatty acid-binding

protein (I-FABP), α-glutathione S-transferase (α-GST), D-lactate, D-dimer, ischemia-modified albumin (IMA), and citrulline. An ideal biomarker needs to be highly specific, highly sensitive, and easily detectable as early as possible in the disease process. The test also needs to be easily measured, inexpensive, and produce rapid results.

I-FABP

I-FABP is particularly interesting as an intestinal ischemia biomarker as it is a small soluble cytoplasmic protein specifically expressed in enterocytes of the mucosal layer in the intestines. I-FABP is also called FABP2 and is named after the gene that expresses it. I-FABP belongs to a family of fatty acid-binding proteins believed to take part in the uptake, metabolism, and transport of long-chain fatty acids. I-FABP is normally undetectable in the peripheral circulation, but studies have shown that intestinal damage by necrosis or inflammation, can quickly give rise to a spike in I-FABP plasma levels.[108-110] It has a very short half-life of about 11 minutes.[111] I-FABP is currently the most studied biomarker for intestinal ischemia.[102]

Citrulline

Citrulline and is an amino acid present in enterocytes in the small intestine, that also has a reasonably short half-life of 3-4 hours. Citrulline is specific to the small bowel and citrulline levels have been proposed to correspond to total enterocyte mass in chronic diseases such as short bowel syndrome and enteropathies.[112] Reduced levels of citrulline are therefore indicative of small bowel dysfunction or chronic diseases such as short bowel syndrome and enteropathies.[113-114] It has also been tested as a marker for acute rejection in intestinal transplants and for detecting acute bowel toxicity after chemo- or radiotherapy.[115-118] Its use as a biomarker for acute intestinal ischemia in patients with acute abdomen has shown a sensitivity and specificity of 39% and 100% respectively.[102]

D-dimer

D-dimer is a routine laboratory test used primarily to rule out deep vein thrombosis or pulmonary embolism in clinical practice. D-dimer is a degradation product of fibrin only elevated by activation of the coagulation cascade. It has a half-life of around 6 hours. D-dimer has also shown promise as a marker of acute intestinal ischemia with high sensitivity.[100, 103-104]

An investigation of the above-mentioned biomarkers for potential use in diagnosing internal herniation was conducted in **Paper IV** of this thesis.

Surgical exploration

Current clinical guidelines recommend a low threshold for surgical exploration when there is a clinical suspicion of IH. This continues to lead to negative explorations which is necessary to avoid potential harm.[77,119] It is also important to stress that patients with ischemic pain, i.e. unbearable pain, need urgent surgical exploration so that a doctor's delay does not lead to irreversible bowel ischemia. There are cases reported where the entire small bowel has been incarcerated into an internal hernia with fatal outcomes.[120] Surgery, either laparoscopic or open, aims to reduce the incarcerated bowel without causing damage to the bowel wall which may easily perforate if not handled with care. (Figure 11) Bowel resection is seldom necessary unless irreversible ischemia and necrosis are seen. Finally, the mesenteric defects are closed with a braided polyester suture, such as Ethibond Excel™ (Ethicon Inc., Johnson & Johnson, Tokyo, Japan) or a similar non-bioabsorbable suture.

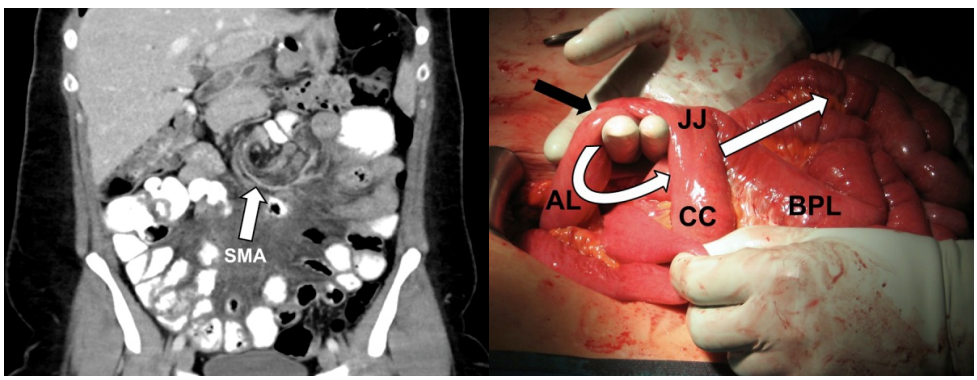


Figure 11. Left: Abdominal CT scan showing torsion of the small bowel mesentery, 'whirlpool sign' (SMA, superior mesenteric artery). Right: Intraoperative picture of herniation of the common channel through the open mesenteric gap (AL, alimentary limb; BPL, biliopancreatic limb; CC, common channel; JJ, jejunojejunostomy; white arrow: direction of the herniation; black arrow: torsion of the small bowel). (Reproduced from Däster, Silvio et al. "Two similar cases of internal hernia after laparoscopic Roux-en-Y gastric bypass surgery." *BMJ case reports* vol. 2013 bcr2013010189. 26 Sep. 2013, doi:10.1136/bcr-2013-010189, Copyright © BMJ Publishing Group Ltd.)

Intussusception

Intussusception occurs most commonly in small children, where the most common form of intussusception, namely ileocecal invagination occurs. This is readily treatable by an enema but may occasionally require surgery in some cases. Intussusception in the adult population is rare, and intussusception involving the small bowel even more so. The few cases that occur are typically caused by a lead point in the form of a polyp, tumor, or adhesion.[121]

Intussusceptions in RYGB-operated patients, on the other hand, is most often jejunal and may involve the jejunojejunostomy (JJ) (Figure 12). Many intussusceptions resolve spontaneously, and their clinical relevance is uncertain. Intussusceptions can, however, in severe cases lead to bowel obstruction with secondary edema, ischemia, and perforation. The cause of these intussusceptions is unknown, and a couple of theories have been proposed. One theory proposes that the jejunojejunostomy may act as a lead point. This is strengthened by the fact that many intussusceptions involve the anastomosis. However not all of them do, leaving the alternative theory about disturbed peristaltic waves more appealing. This theory states that the Roux-limb and biliary limb have a mismatch of the peristaltic waves that meet at the jejunojejunostomy. This disturbance is caused by the discontinuity of the small bowel. The pacemaker cells in the duodenum propagate a peristaltic wave that only reaches the anastomosis, while the remaining small bowel will have irregular peristalsis because of independent pacemaker cells that are cut off from the duodenum. The irregular waves could cause the bowel to invaginate randomly but more frequently near the anastomosis where the two limbs meet.[122]

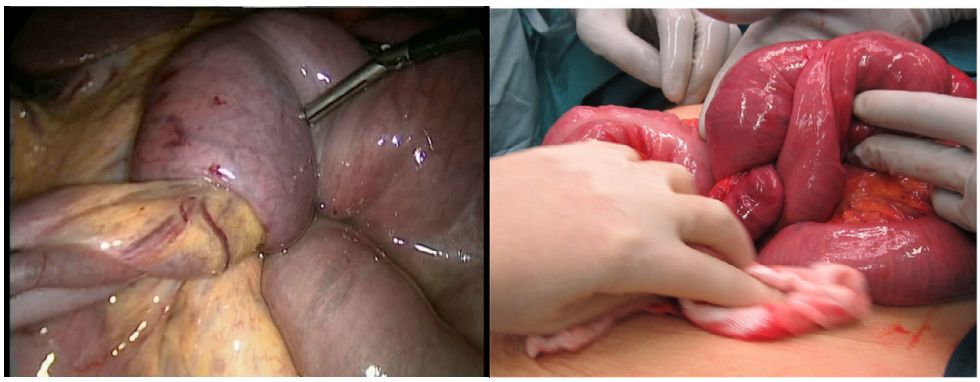


Figure 12. Laparoscopic (left) and open (right) surgery for small bowel intussusception in RYGB patients.

A CT finding of small bowel intussusception is not uncommon in the RYGB patient, but the clinical implication may be unclear. Whether intermittent intussusceptions are symptomatic or not is unknown. That an intussusception may cause bowel obstruction and be a surgical emergency is clear, but the radiological correlation of asymptomatic small bowel intussusceptions is unclear. This was the basis for the fourth paper in this thesis. The surgical treatment of intussusceptions is debated, and no consensus currently exists. Necrotic bowel obligates resection, however, in cases with viable bowel after reduction it remains unclear whether a simple reduction, an enteropexy, or

resection should be performed.[123-125] Some proponents of the peristaltic wave theory argue in favor of a remodeling of the jejunojejunostomy from an anti-peristaltic to an isoperistaltic direction in an attempt to reduce the risk of recurrence, which has been a model used by bariatric surgeons at our University Hospital.

Marginal ulcer

Marginal ulcer, or stomal ulcer, can occur at the gastroenterostomy and present as either an early or late complication. The incidence rates in the literature vary from 0.6% to 16%, while SOReg has reported rates consistently below 2% in Sweden.[126-128] The ulcers occur more frequently in men and smokers. Recommended treatment includes proton pump inhibitors, sucralfate, and cessation of smoking. The low incidence rate in Sweden is thought to be explained by our comparatively small gastric pouches, as studies have shown that a smaller gastric pouch lowers the risk.[129] Marginal ulcers are important as they may cause acute gastrointestinal bleeding or perforation. Perforation can lead to peritonitis and sepsis, which may be life-threatening. Chronic ulcers may be the cause of stricture development, which may require recurrent endoscopic dilatation or stent treatment.[130-131] Strictures are more common after end-to-end anastomosis than hand-sewn or horizontal staple lines.

Gallstone disease

Both obesity and post-surgical weight loss contribute to the high incidence of gallstones in patients with bariatric surgery. Subsequently, these patients have a higher incidence of cholecystectomy.[132-134] The Roux-en-Y anatomy further complicates the management of common bile duct stones as a standard endoscopic retrograde cholangiography procedure is no longer possible. Common bile duct (CBD) stones are encountered with intraoperative cholangiography in 7-18% of laparoscopic cholecystectomies but are more frequent in the acute setting (Figure 13).[135-136] Alternative techniques for the management of CBD stones are therefore needed, such as laparoscopy-assisted transgastric ERC or laparoscopic transcystic common bile duct exploration.

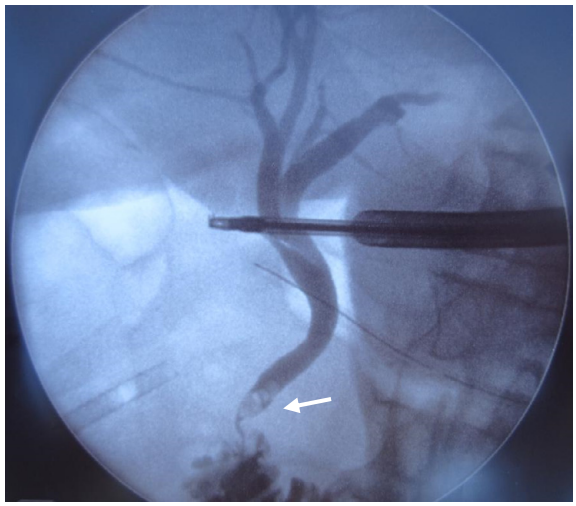


Figure 13. Intraoperative cholangiogram identifying multiple common bile duct stones (arrow) and a dilated biliary tree (Courtesy of Ulf Pettersson).

Laparoscopy-assisted transgastric ERC

Laparoscopy-assisted transgastric ERC (tERC) was specifically developed for the Roux-en-Y anatomy and first reported in 2002.[137] The technique has shown promising results at experienced centers and has also been evaluated in Sweden.[138-143] tERC is, in short, a standard or rendezvous ERC performed through a trocar placed into the remnant stomach under laparoscopic visualization and is similar to the laparoscopic construction of a gastrostomy (Figure 14).

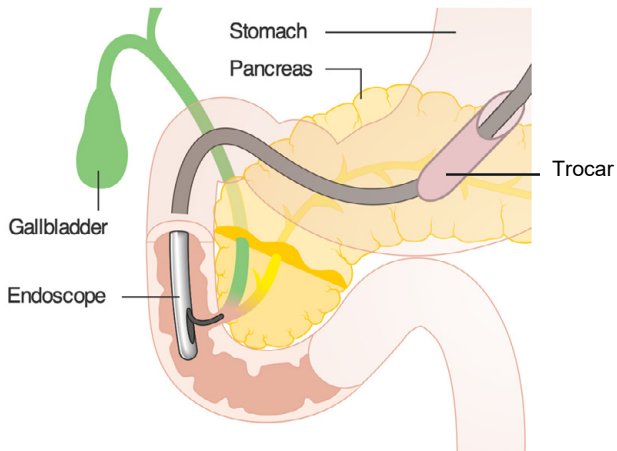


Figure 14. Diagram of transgastric endoscopic retrograde cholangiography (tERC). (By Cancer Research UK - Original email from CRUK, CC BY-SA 4.0, https://commons.wikimedia.org/w/index.php?curid=34332566 modified with trocar for transgastric access).

Laparoscopic transcystic common bile duct exploration

Another technique for managing CBD stones is the laparoscopic transcystic common bile duct exploration (LTCBDE), first described in 1993.[144] This technique has also shown promising results at experienced centers and has the benefit of being a minimally invasive option for all patients.[145-147]

LTCBDE is performed with the operating surgeon and an assistant at their normal positions on the patient's left side. An additional 5 mm long trocar is placed under the right costal margin in the midclavicular line to achieve proximity to the cystic duct. An introducer and a guidewire may be used to facilitate entry into the cystic duct. A winding cystic duct may require dilatation using a balloon catheter to allow for the passage of the endoscope. A 2.8mm (8.5 Fr) choledochoscope (KARL STORZ SE & Co. KG:s, Tuttlingen, Germany) is entered through the cystic duct whereby the CBD is visualized by continuous saline infusion (Figure 15). Small stones may be extracted or flushed out into the duodenum. Stone extraction is performed using retrieval baskets, e.g. Gemini® or Zero-tip® (Boston Scientific, MA, USA). Larger and more complex stones may be fragmented by the retrieval baskets or using laser lithotripsy.[148]

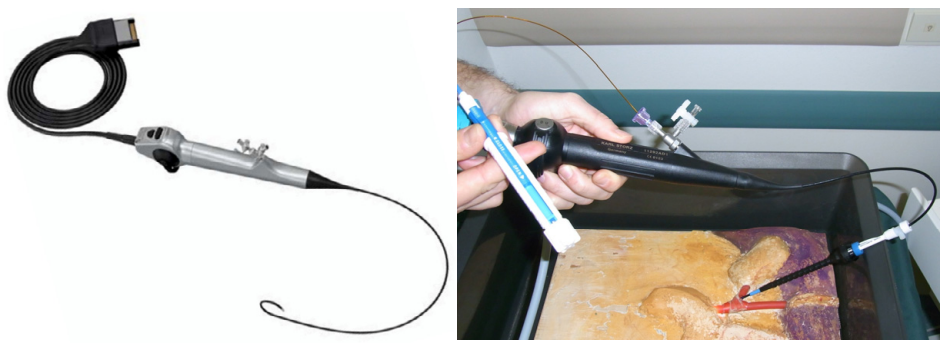


Figure 15. Left: A 2.8mm choledochoscope (KARL STORZ SE & Co. KG:s, Tuttlingen, Germany). Right: Model of LTCBDE showing a choledochoscope with a retrieval basket and an introducer entered into the cystic duct of a simulated biliary tree. (Picture courtesy of Ulf Pettersson)

Another variant of the technique is the insertion of the choledochoscope through a choledochotomy to enable easier access to the CBD in the event of large stones or a narrow cystic duct.[149] The drawbacks of a choledochotomy are the risk of bile leakage and stricture formation. This technique has not, as far as we know, been implemented in Sweden.

No previous study has, to the best of our knowledge, compared outcomes between laparoscopy-assisted transgastric ERC and laparoscopic transcystic common bile duct exploration for Roux-en-Y gastric bypass operated patients. This, therefore, became the topic of **Paper V**.

Aim and Objectives

The overall aim of this thesis was to investigate late surgical complications to Roux-en-Y gastric bypass (RYGB) surgery experienced by acute care surgeons to improve the diagnosis and management of such conditions.

Specific objectives:

I. To investigate the overall management and outcomes of Roux-en-Y gastric bypass operated patients admitted for acute abdominal pain at Skåne University Hospital in Malmö from April 2012 to June 2015. A secondary aim was to evaluate how often the admissions were caused by a late complication to the Roux-en-Y gastric bypass.

II. To investigate long-term follow-up and recurrence risk after surgery for internal herniation at Skåne University Hospital in Malmö and find factors influencing the risk of recurrence. A secondary aim was to compare the outcomes of patients treated by acute care surgeons to those treated by bariatric surgeons.

III. To investigate the potential use of the ischemia biomarkers citrulline, intestinal fatty acid-binding protein (I-FABP), and D-dimer and the routine biomarkers C-reactive protein (CRP), white blood cell count (WBC), and lactate in serum for diagnosing internal herniation in Roux-en-Y gastric bypass operated patients with acute abdominal pain. A secondary aim was to compare self-reported pain intensity and duration for patients with or without internal herniation in this cohort.

IV. To correlate radiological findings of intussusceptions in acute abdominal computed tomography scans of Roux-en-Y gastric bypass operated patients with the clinical outcomes to differentiate intussusceptions requiring emergent surgery for small bowel obstruction.

V. To compare laparoscopic transcystic common bile duct exploration and intraoperative endoscopic retrograde cholangiography for the single-stage management of common bile duct stones in Roux-en-Y gastric bypass operated patients using national registry data for 2011-2020.

Materials and Methods

The thesis began by prospectively including all Roux-en-Y gastric bypass operated patients admitted to the acute surgical wards at Skåne University Hospital in Malmö, Sweden in a quality assurance program from April 2012. Ethical approval for the studies was soon approved and a Ph.D. project plan was laid out for retrospective analysis of the patients in the descriptive **Paper I**, which would enable us to get an overall understanding of the various complications that affect the Roux-en-Y operated patients. Later a long-term follow-up of the patients with the most common complication, internal herniation, was conducted in **Paper II**. Internal herniations were also studied further in **Paper III**, by performing a prospective clinical study of biomarkers and a pain questionnaire. In this study patients were enrolled at admission and permission was sought for blood sampling at admission and at the time of surgery. The patients were also asked to fill in a simple pain questionnaire. **Paper III** was planned to start immediately after the descriptive study in **Paper I** had finished its inclusions.

The region of Skåne is particularly suitable for studying acute care handling of Roux-en-Y gastric bypass operated patients because of the high frequency of Roux-en-Y gastric bypass surgeries. In the past decade, the frequency of RYGB operations was about 80 per 100,000 inhabitants annually. In addition, medical records for all hospitals in Region Skåne are accessible through the medical record system Melior/SIEView (© 2022 Oracle, Austin, TX, United States), which includes all emergency departments and acute surgical wards in the region.

Paper IV was a collaboration with our radiologists after having observed an increased number of abdominal computed tomography scans with intussusception findings in RYGB-operated patients with abdominal pain. While clinical experience has shown that many intussusceptions do not seem to have any clinical correlation, some resulted in severe bowel obstruction requiring emergent surgery. In collaboration with our radiologists, we decided to conduct a retrospective study comparing the radiological findings with the clinical outcome.

Paper V focused on the challenge of managing common bile duct stones in RYGB-operated patients with gallstone disease. As the bypassed stomach and duodenum hinder normal access to the duodenum for a standard ERC, alternative techniques need to be used.

A comparison was made between the two most common surgical techniques for dealing with common bile duct stones in RYGB-operated patients, laparoscopic transcystic common bile duct exploration and intraoperative endoscopic retrograde cholangiography. National quality registries GallRiks, for the treatment of gallstone disease, and SOReg, the Scandinavian Obesity Surgery Registry, were matched to find and compare RYGB-operated patients with intraoperative findings of common bile duct stones during cholecystectomy. Those treated by either single-stage laparoscopic transcystic common bile duct exploration or endoscopic retrograde cholangiography were compared.

Statistical methods

All databases and calculations for the included studies were stored and analyzed using SPSS Statistics version 25-28 (IBM Corporation, Armonk, NY, USA). For all statistical analyses a two-sided ρ-value of ≤.05 was considered statistically significant.

The studied cohorts in all studies were relatively small and could not generally be considered normally distributed. Continuous variables were therefore usually reported as median with minimum and maximum values or interquartile range. The preferred statistical method for comparisons of two groups was the Mann-Whitney U test, also called the Wilcoxon Rank Sum Test. Similarly, for the comparison of more than two groups, the Kruskal-Wallis test was used. These methods make statistical comparisons of the median of independent populations with the assumption of similar distribution. However, no assumption is made of normal distribution. For the comparison of categorical values, Pearson's Chi-Squared (χ^2) test was used for values greater than 5, otherwise, Fisher's Exact test was used. For evaluation of the diagnostic test in Paper IV, specificity and sensitivity were calculated as well as positive predictive value and negative predictive value. For the comparison of inter-rater variability in **Paper IV**, I used Spearman's Rho (ρ), which is a non-parametric test used to measure the strength of association between two non-normally distributed scale variables. I also used Cohen's kappa (κ) in **Paper IV** to measure interrater agreement between the two radiologists' grouped measurements.

All tests are described in more detail below.

Mann-Whitney U test

The Mann-Whitney U test, also called Wilcoxon Rank Sum Test, compares differences between two independent groups when the dependent variable is either ordinal or continuous but does not need to be normally distributed. The test compares the distributions and tells us whether two samples are drawn from the same population.

The test makes four assumptions:

I. The dependent variable needs to be ordinal or continuous.

II. The independent variable needs to be two independent groups.

III. The observations need to be independent.

IV. To interpret the results, you need to know if the distribution in both groups is similar. If the distribution is similar, the test reports a difference in the median, otherwise, it reports a difference in mean rank.

Kruskal Wallis test

The Kruskal Wallis test is similar to the Mann-Whitney U test in testing whether two or more samples are drawn from the same population. It makes all the same assumptions but can be used to compare more than two groups. It also compares the median between the groups if they have a similar distribution, otherwise the mean rank.

Pearson's Chi-Squared test (χ^2)

A chi-squared test is a non-parametric test of categorical variables used to test if the observed frequency differs from the expected frequency. It can be used either as a goodness of fit test where all outcome is assumed to be the same and the test will tell whether they are significantly different from what is expected. It can also be used as a test of independence between groups, i.e. that the observed frequency differs from the expected frequency between two or more groups.

The test assumes:

1. Testing a hypothesis about one or more categorical variables, not continuous variables. Continuous variables would have to be categorized into intervals to use the test.
2. A random sample from the population.
3. A minimum of 5 observations in each group.

$$\chi^2 = \sum \frac{(O - E)^2}{E}$$

The equation for calculating the chi-squared (above) is used to look up the probability in a chi-square distribution table.

Fisher's Exact test

Fisher's Exact test is used in the analysis of contingency tables similar to the chi-squared test. It is, however, robust even for numbers smaller than 5 and therefore often used for small sample sizes. It does however work for all sample sizes. The test was devised by Ronald Fisher for the famous "lady tasting tea" experiment reported in 1935.[150] He reported that he had set up an experiment of preparing eight cups of tea in which half had milk poured onto the tea and the other half had tea poured onto milk. Lady Muriel Bristol had stated that she could identify them by tasting the difference, which she did!

Spearman's Rho (ρ)

Spearman's rank correlation coefficient or Spearman's Rho (ρ) is a non-parametric test used for calculating the strength of association between two non-normally distributed continuous or ordinal variables. It is a nonparametric measure of rank correlation.

Cohen's kappa (κ)

Cohen's kappa (κ) is used as a quantitative measure of inter-rater reliability, also called an interobserver agreement, of two qualitative variables. It takes into account the possibility of agreement occurring by chance. The formula is:

$$\kappa = \left(\frac{\rho_o - \rho_e}{1 - \rho_e}\right)$$

Where ρ_o is the observed agreement, and ρ_e is the expected agreement. The values will always be less than or equal to 1. A value less than zero indicates no agreement, 0–0.20 is slight, 0.21–0.40 is fair, 0.41–0.60 is moderate, 0.61–0.80 is substantial, and 0.81–1 is almost perfect agreement in the most commonly used interpretation.

Ethical approval

Paper I-IV received ethical approval from the Regional Research Ethics Committee in Lund, Sweden. **Paper I & III** (Dnr. 2014/308) and **Paper II & IV** (Dnr. 2019/03583). **Paper V** was approved by the Swedish Ethical Review Authority (2021-05564-01).

Paper I

Paper I, was a retrospective observational study. All consecutive Roux-en-Y gastric bypass operated patients admitted for acute surgical care from April 2012 to June 2015 were prospectively included in a database. Inclusion criteria were: adult patient with previous Roux-en-Y gastric bypass operation admitted for acute surgical care. Exclusion criteria were: referrals with transfer from other hospitals, referrals to the primary bariatric center for continued treatment, reversal of the gastric bypass surgery, or any cause for admission other than abdominal pain. Ethical approval was obtained from the Regional Research Ethics Committee in Lund, Sweden (Dnr. 2014/308), but no informed consent was required for this type of study.

For the analysis, patients were grouped into early (≤30 days) or late (>30 days) admission after RYGB. I then reviewed the medical records for the RYGB surgery. The date of surgery, anthropometric measures, whether the surgery was laparoscopic or open, and whether the mesenteric gaps were closed or not were recorded.

Admissions data

Data from admission records of the date of admission, anthropometric measure, medical history, previous closure of the mesenteric gaps, and length of stay were noted. Body Mass Index (kg/m^2), % Excess Weight Loss (%EWL), and time since RYGB surgery were then calculated from the available data.

For each patient, the number of abdominal diagnostic examinations was noted, such as computed tomography scans, ultrasound scans, magnetic resonance cholangio-pancreatographies, and gastroscopies.

Acute surgeries

Operation charts were investigated for the operation performed, surgical diagnoses, the bariatric competency of the main surgeon, whether surgery was performed during on-call hours, if surgery was performed laparoscopically, needed to be converted or was planned as an open procedure, and whether open mesenteric gaps were found during surgery.

After chart review, each surgery was categorized as:

I. RYGB complication
   Defined as surgeries for any complication to the previous RYGB surgery, such as internal herniations, incisional hernias, perforated marginal ulcers, postoperative bowel obstruction, or intussusceptions.

II. Other surgery
Included all common surgical conditions, e.g. appendicitis or cholecystitis, that were unrelated to the RYGB procedure.

III. Unremarkable laparoscopy
Defined as explorative laparoscopies, with no pathological findings to treat or explain the patient's preoperative condition. These were mainly performed to rule out RYGB complications such as internal herniation or adhesions.

Any open mesenteric gaps found during surgery were routinely closed with running braided non-bioabsorbable sutures and separately noted in the database.

Postoperative complications

Postoperative complications were classified using a simplified Clavien-Dindo classification, with grades I-V (Table 1).[150]

Table 1: The Clavien-Dindo classification of postoperative complications. (Copyright © 2022 AssesSurgery GmbH)

Grades	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade III	Requiring surgical, endoscopic or radiological intervention
Grade IV	Life-threatening complication (including CNS complications) requiring IC/ICU-management With single or multiorgan dysfunction (including dialysis)
Grade V	Death of a patient

Patients not requiring surgery

The discharge diagnosis was categorized for patients discharged without having undergone surgery during the admission. The Swedish version of the International Statistical Classification of Diseases and related health problems, tenth revision (ICD 10-SE) was used for categorization into the following categories:

I. Unspecific abdominal pain (R10.1-4)

II. Gallstone disease (K8x.x)

III. Other specified diseases (e.g. kidney stone, urinary tract infection)

Follow-up

The follow-up period was reviewed for all surgical re-admissions, acute surgeries, and overall mortality until October 17th, 2018. The surgeries were categorized as RYGB-complication or not, while surgery for internal herniation was specifically noted.

Paper II

Paper II was a retrospective observational study of Roux-en-Y gastric bypass operated patients undergoing surgery for an internal herniation between April 2012 and December 2015 at Skåne University Hospital in Malmö or Lund. Patients were extracted from the databases obtained from the retrospective study, Paper I, and the prospective study, Paper III. The internal herniation was verified in the operation charts as requiring manual repositioning of incarcerated bowel. Laparoscopy with simple closure of mesenteric gaps but without herniated bowels was not included. Exclusion criteria were previous surgery for internal herniation and reversal of the Roux-en-Y anatomy. Ethical approval was obtained from the Regional Research Ethics Committee in Lund, Sweden (Dnr. 2019/03583), but no informed consent was required for this type of retrospective study.

Medical chart review

Medical charts were reviewed for demographic and anthropometric data, such as sex, age, and total weight loss % (TWL%) since RYGB surgery. Medical charts for the RYGB surgery were sought after and the date for the RYGB surgery and information on whether the mesenteric gaps were closed were recorded. Operation charts of the internal herniation surgery were reviewed to determine whether the internal hernia occurred in Petersen's space or beneath the jejunujejunostomy and to note whether the surgeon was an acute care surgeon or a bariatric surgeon. It was also noted if the surgery was laparoscopic, converted, or open.

Follow-up

Each patient's digital medical record was followed until December 31st, 2019 for any emergency department visit(s), readmission(s), or surgery for recurrence of internal herniation. For any additional surgery of internal herniation, it was noted which mesenteric gap that the herniation had occurred in. In addition, the total number of abdominal computed tomography scans performed during follow-up was recorded.

Paper III

For paper III, RYGB patients admitted for acute abdominal pain between June 2015 and December 2017 were prospectively included. The inclusion criteria were: ≥18 years of age, able to understand and give written consent, and admitted for acute abdominal pain within the previous 72 hours. The included patients signed an informed consent form at admission to allow for the study group to review their medical charts, draw blood samples at admission and at the time of surgery, as well as answer a medical history and pain assessment questionnaire for the purpose of this study.

Biomarkers

Blood samples for analysis of citrulline, Intestinal fatty acid-binding protein (I-FABP), and D-dimer, were drawn <72 hours from admission, before any acute surgery, and immediately centrifuged, frozen and stored at -80º Celsius. Levels of white blood cell count (WBC), C-reactive protein (CRP), and lactate from standard admission blood sampling were obtained through the chart review.

Biomarker analysis was performed by an independent technician according to the manufacturer's instructions. All serum samples were dethawed simultaneously and batch analysis of the biomarkers was performed with commercially available ELISA kits for Citrulline (MyBiosource Inc., San Diego CA, USA; MBS2601236), I-FABP (Hycult Biotechnology, Uden, The Netherlands; HK406), and D-dimer (Abcam, Cambridge MA, USA; ab260076).

Questionnaire

Patients were asked to fill in a questionnaire with binary (yes/no) questions about the following comorbidities: cardiovascular disease or hypertension, diabetes, pulmonary disease, psychiatric disease or substance abuse, or any chronic pain disease such as arthritis, fibromyalgia, or lumbago. The questionnaire also asked the patients for a pain assessment with two numeric rating scale (NRS) questions about the level of pain at pain onset and admission. We also asked patients to report when the pain had started.

Chart review and categorization

Medical records and operation logs were retrospectively reviewed for demographic data, diagnostic CT scans, surgery, and diagnosis at discharge. Readmissions within 30 days with discharge diagnosis at readmission were recorded. Patients were categorized into four categories based on findings at surgery and/or discharge diagnosis.

I. Internal herniation
Defined at surgery as an incarcerated bowel herniating through either mesenteric defect, i.e. Petersen's space or beneath the jejunojejunostomy, requiring manual reduction at the surgery.

II. Small bowel obstruction
Defined as a small bowel obstruction at the surgery of any cause other than an internal herniation.

III. Other specified diagnoses
Defined as a patient discharged with any specified diagnosis other than unspecified abdominal pain (R10.x in ICD-10-SE).

IV. Unspecified abdominal pain
Defined as a patient discharged with a diagnosis of unspecified abdominal pain (R10.x in ICD-10-SE), despite diagnostic workup and/or explorative surgery.

Paper IV

For paper IV, a collaboration with our radiology department was established. Professor Olle Ekberg and radiologist dr. Daisy Lee kindly agreed to a study of the clinical correlation of intussusception findings in Roux-en-Y gastric bypass operated patients. Ethical approval was obtained from the Regional Research Ethics Committee in Lund, Sweden (Dnr. 2019/03583), but no informed consent was required for this type of retrospective study.

Database search

A database search for acute abdominal computed tomographies (CT) reporting intussusceptions in Roux-en-Y gastric bypass operated adults between 2012-2019 at Skåne University Hospital in Malmö, Sweden was performed. The radiology database RIS/PACS (Sectra AB, Linköping, Sweden) was searched with the following terms: "gastric bypass" or "GBP" in the referral and for "invag" (short for invagination: Swedish for intussusception) in the radiology report. The results were then manually reviewed to exclude all reports with negating findings, i.e. where the radiologist reported that no intussusception was found. Any patient that did not have a Roux-en-Y anatomy was excluded, i.e. either because of mistakes in the referral or because a patient had her anatomy reversed.

Radiological re-evaluation

The two above-mentioned independent radiologists with vastly different experience-levels (42 and 1 year(s) since board approval) re-evaluated the CT scans using a predefined protocol (see below). At first, the scans were checked for adequate quality, usage of oral and/or intravenous iodine contrast (Omnipaque; GE Healthcare AB, Danderyd, Sweden), and verification of the intussusception.

The questions evaluated (variables) were:

I. Is the intussusception located in the left upper quadrant (LUQ)?
The jejunojejunostomy is located in the left upper quadrant and has been suggested as the culprit lead-point for symptomatic intussusceptions. Hence, this variable was used as a substitute for the intussusception being in the vicinity of the jejunojejunostomy.

II. Does the intussusception cause proximal bowel dilatation?
Proximal bowel dilatation is a common sign of small bowel obstruction.

III. Has positive oral contrast passed through the intussusception?
Positive oral contrast that does not pass through the intussuscepted bowel may indicate bowel obstruction.

IV. Measurement of the length of the intussusception in millimeters (mm).
The longest measurement in either plane was used to measure the length of the intussusception in millimeters.

V. Signs of an internal herniation?
A diagnosis of internal herniation was determined at the radiologists' discretion by identifying one of many typical signs, such as e.g. "Whirl pool sign" or SMV (superior mesenteric vein) sign.

Medical chart review

The medical charts were separately reviewed to extract admissions data of the cohort. Time since RYGB was noted as well as admission symptoms such as acute and chronic abdominal pain, nausea and vomiting. The operation charts were reviewed to determine if an intussusception and bowel obstruction was diagnosed and if the intussuscepted bowel needed manual reduction. Discharge summaries were reviewed to determine the final diagnosis and whether the radiological finding of intussusception was considered an incidental finding or not.

Categorization of intussusceptions

Based on the chart review, the cohort was grouped into three categories; Acute intussusception, intermittent intussusception, or incidental intussusception.

I. Acute intussusception
Defined as a patient with a clinical presentation requiring emergent surgery within 24 hours of admission.

II. Intermittent intussusception
Defined as a surgical admission with a discharge diagnosis of intussusception but not requiring emergent surgery within the first 24 hours of admission. These patients may or may not have undergone explorative surgery during the admission.

III. Incidental intussusception
Defined as a patient whose intussusception finding was considered incidental, that either did not require admission or was discharged with a different diagnosis.

Paper V

Ethical approval was obtained by the Swedish Ethical Review Authority (2021-05564-01) for a national registry-based study. The study was designed to include adults (≥18 years old) with a history of a Roux-en-Y gastric bypass operation, that subsequently had a cholecystectomy with an intraoperative finding of common bile duct stones. This cohort was retrieved by cross-matching data from the Swedish Registry for Gallstone Surgery and ERCs, GallRiks (n=215,670), and the Scandinavian Obesity Surgery Registry, SOReg (n=60,479). Data were extracted for the 10-year period 2011-2020. Exclusion criteria were any indication other than gallstone-related for the cholecystectomy, reversal of the Roux-en-Y anatomy before the cholecystectomy, and if the cholecystectomy was not the primary operation.

The SOReg database was solely used to select patients with a Roux-en-Y gastric bypass that had not been reversed before to the cholecystectomy, while the original variables extracted from GallRiks are presented with their explanation in Table 2 (in Swedish).

The preoperative variables included the patient's age, sex, length in centimeters, weight in kilograms, the name of the hospital, and the ASA score given by the anesthesiologist.

Surgical variables included the date of surgery, if surgery was elective or acute, if the patient had preoperative raised bilirubin or icterus, if the patient had acute cholecystitis

or pancreatitis, if the surgery was laparoscopic, converted, or open, if surgery was performed outside of office hours, and the operation time in minutes. The size of the largest common bile duct stone was obtained from an ordinal variable in groups of <4mm, 4-8mm, and >8mm.

The variable for the treatment method of common bile duct stones was used to identify patients treated by single-stage intraoperative ERC or laparoscopic transcystic common bile duct exploration. The GallRiks variable, "Peroperativ ERCP", however, does not differentiate between different techniques of performing the intraoperative ERC, i.e. laparoscopy-assisted transgastric or using push-enteroscopy. A clinical assumption was made, based on practical knowledge of available surgical and endoscopic techniques in Sweden, that the procedures were most likely performed using laparoscopy-assisted transgastric access.

The intraoperative surgical complications were reported in the two binary variables: Intraoperative complication and Bowel perforation. The postoperative complications were reported in the following binary variables: Abscess, Bleeding, Bile leak, Residual stones, and Cholangitis. Readmissions, reoperations, and an ERC within 30 days were also recorded.

The included cohort and outcome variables of the two techniques were compared.

Table 2 Original variables from the national registry Gallriks (Swedish).

	Registrering	Variabel	Variabeltext	Registret hjälptext
Preop	DATEOFTREAT	Behandlingsdatum		
Preop	ASA	ASA-klass	1=Helt frisk | 2=Mild till moderat systemsjukdom | 3=Svår systemsjukdom | 4=Livshotande sjukdom | 5=Moribund med liten chans till överlevnad	Använd anestesins bedömning gällande ASA-klassificering
Preop	ANGELAGENHETSGRAD	Akut/elektiv vård	1=Elektiv | 2=Akut inlagd (åtgärd utförd under samma vårdtillfälle) | 3=På vitalindikation (hotande kliniskt tillstånd)	Elektiv = planerad vård Akut inlagd = operation/ERCP av kliniska/praktiska skäl under samma vårdtillfälle t.ex. hopade gallstensanfall, måttlig kolecystit På vitalindikation = kliniskt tillstånd som kräver op/ERCP inom 12 tim t.ex. tilltagande peritonit vid kolecystit/pankreatit/kolangit
Preop	PATLANGD	Längd (cm)	50-250	Patientens längd i cm.
Preop	PATVIKT	Vikt (kg)	10-300	Patientens kroppsvikt i kg.
Preop	BMI	BMI		Body Mass Index = vikt / (längd x längd) vikt i kilogram, längd i meter
Operation	AKUTKOLECYSTIT_OP	Pågående akut kolecystit	1=Nej | 2=Ja	Klinisk bedömning utifrån status, temp och laboratorievärden.
Operation	AKUTPANCREATIT_OP	Pågående akut pankreatit	1=Nej | 2=Ja	Klinisk bedömning utifrån status, temp och laboratorievärden.
Operation	IKTERUS_OP	Pågående bilirubinstegring/ koledockussten	1=Nej | 2=Ja	Klinisk ikterus/totalbilirubin >30 (µmol/l) eller känd koledockussten
Operation	OPERATION_OP	Operationsmetod	1=Laparoskopisk kolecystektomi | 2=Laparoskopisk konverterad till öppen | 3=Öppen kolecystektomi | 4="Minigalla" (< 8cm hudsnitt) | 5=Öppen koledokotomi (tid kolecystektomerad) | 6=Annan operation (=subtotal kolecystektomi) | 7=Laparoskopisk subtotal kolecystektomi | 8=Öppen subtotal kolecystektomi | 9=Robotassisterad kolecystektomi | 10=Avbryter utan att slutföra kolecystektomin | 11=Avbryter laparoskopisk operation | 12=Avbryter öppen operation | 13=Avbryter konverterad operation	
Operation	STENDIAM_OP	Storlek största sten	3=<4 mm | 2=4 - 8 mm | 1=>8 mm	Storlek på största koledokussten uppskattat från perop kolangiografi
Operation	TERAPIKOLEDOKUSSTEN_OP	Behandling av koledokussten	1=Förbereder för postoperativ ERCP | **2=Peroperativ ERCP** | 3=Laparoskopisk koledokotomi | **4=Transcystisk stenextraktion** | 6=Spolad/manipulerad ut i tarmen | 5=Öppen koledokotomi | 0=Ingen peroperativ åtgärd	Den teknik som till slut krävts för stenfrihet/sista åtgärden. Om ERCP - gå till ERCP-protokollet med knappen längs ner på sidan.
Operation	OPTID_OP	Operationstid (minuter)	0-600	Ange den s.k. knivtiden i minuter. Om ERCP görs peroperativt så ska tiden för ERCP räknas in i den totala operationstiden. ERCP- tiden startar när man börjar sin intubation med duodenoskopet och avslutas när duodenoskopet utförskaffas. Ställtiden tilldelas kolecystektomin.
Operation	JOURTID_OP	Jourtid	1=Ja | 2=Nej	Jourtid definieras som hela eller del av operationen utanför ordinarie arbetstid
Operation	PEROPCOMPLICATION_OP	Perop komplikation	1=Nej | 2=Ja	
Operation	PERFORTARM_OP	Perforerad tarm	1=Nej | 2=Ja	Peroperativt perforerad tarm.
30-dagars-uppfölj.	ABSCESS_30D	Infektion med abscess	1=Nej | 2=Ja	Infektion som krävt åtgärder som t.ex. antibiotikabehandling etc. För registrering av behandling se nedan.
30-dagars-uppfölj.	ANNANPOSTOPKOMPL_30D	Annan komplikation		
30-dagars-uppfölj.	BLODNING_30D	Blödning	1=Nej | 2=Ja	Blödning som krävt åtgärd t.ex. transfusion eller/och reoperation.
30-dagars-uppfölj.	GALLHINDER_30D	Gallvägsobstruktion/icterus/kvarsten	1=Nej | 2=Ja	Ikterus som krävt åtgärd
30-dagars-uppfölj.	GALLACKAGE_30D	Galläckage	1=Nej | 2=Ja	Galläckage till bukhålan som krävt åtgärd
30-dagars-uppfölj.	KOLANGIT_30D	Kolangit	1=Nej | 2=Ja	Gallvägsutlöst sepsis
30-dagars-uppfölj.	ATERINLAGGNING_30D	Oplanerad återinläggning inom 30 dagar	1=Nej | 2=Ja | 0=Uppgift saknas	-
30-dagars-uppfölj.	ERCPBEHKOMPL_30D	ERCP-behandling	1=Nej | 2=Ja | 3=Ja, endast kartläggning | 4=Ja, stentinläggning | 5=Ja, stentextraktion | 6=Ja, stenextraktion | 7=Ja, flera åtgärder	Komplikationen behandlades med ERCP
30-dagars-uppfölj.	REEXPLORATION_30D	Reoperation	0=Nej | 1=Ligatur av gallgång (JKB96) | 2=Sutur av gallgång (JKB40) | 3=Hepatico-jejunostomi (JKD20, JKD30) | 4=Annan rekonstruktion (JKD96) | 5=Enbart exploration och dränering (JAH00, JWC00, JWB00) | 6=Utrymning av hematom/blodstillning (JWE00, JWD00) | 7=Annat	Komplikationen ledde till reoperation för rekonstruktion av gallvägar, blodstillning, dränering etc.

Results and Comments

Paper I

The inclusion criteria were met by 282 out of 300 consecutive patients admitted for acute surgical care at Skåne University Hospital in Malmö from April 2012 to June 2015. After analysis of time since their RYGB surgery, their admissions were divided into groups of early (≤30 days) admission (n=18) and late (>30 days) admission (n=264). The flowchart (Figure 1) shows the management and outcome of the studied cohort.

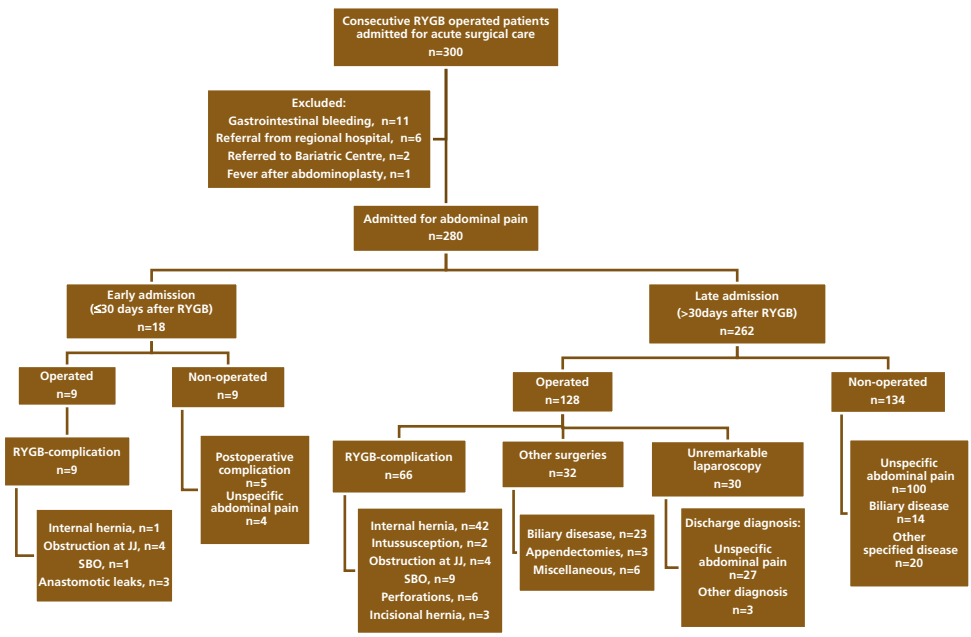


Figure 1. Flowchart of the acute surgical care management of acute abdominal pain in Roux-en-Y gastric bypass patient

Early admission

Nine patients in the early admissions group required emergency surgery for RYGB complications; obstruction at the jejunojejunostomy (n=4), anastomotic leak (n=3), internal herniation (n=1), and other small bowel obstruction (n=1). The remaining nine patients were treated conservatively. Five patients were treated for various postoperative complications while four patients were observed for unspecific postoperative abdominal pain.

Late admission

The main focus of this article was to record the outcomes of patients admitted late (>30 days) after their RYGB surgery. Acute operations were performed on 128 out of 262 patients admitted late after their RYGB. Operations for RYGB complications (n=66) were the most common, while 30 patients underwent unremarkable explorative laparoscopies. The remaining 32 patients had common surgical diagnoses.

Notably, one patient was operated on twice. First, an unremarkable laparoscopy was performed to rule out an acute internal herniation where no pathology was found. However, the open mesenteric gaps were nevertheless closed as per routine during the surgery. Later, during the same hospital admission, it became apparent that the patient developed cholecystitis for which the patient underwent a subacute cholecystectomy. This patient is reported under "Others surgery" and "Biliary disease" as cholecystitis became the main discharge diagnosis. The distribution of surgeries are illustrated in Figure 2.

The RYGB surgery had been performed laparoscopically in 93 % of patients. No significant differences were found in patient groups regarding sex distribution, age or BMI at admission, BMI at GBP, or time since RYGB surgery (Table 1, 2). Weight loss data were available for 65% of patients, and showed a median %EWL of 76.7, and BMI loss of 11.5 kg/m^2 without significant differences between the categories.

The medical history of the patient cohort was largely unremarkable with no differences between the group. Our observation that more than 1 in 10 patients had a chronic pain disease suggested that this condition was overrepresented in our cohort.

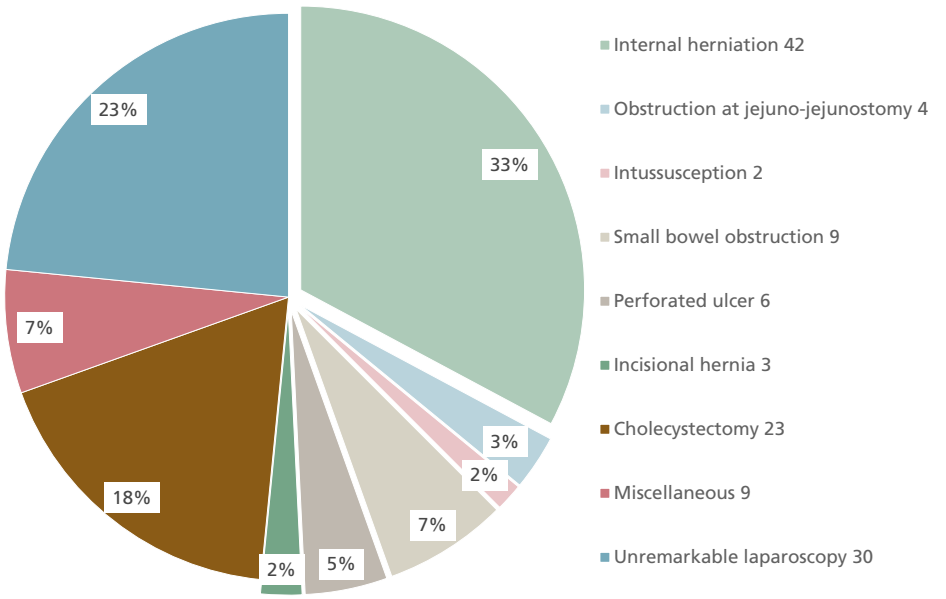


Figure 2. Pie charts illustrating the distribution of surgical diagnoses of all acute surgeries (n=128) for RYGB-operated patients with late admissions for acute abdominal pain. The RYGB complication slices are separted.

RYGB complications

Open mesenteric gaps were diagnosed in 58% (73/128) of all operations, despite 52% of them reporting prior closure of the gaps (Table 2, 3). Internal herniation (n=42) was by far the most common RYGB complication requiring surgical treatment. The internal herniations either had truly incarcerated bowel (n=37), bowel ischemia (n=3), or chylous ascites (n=2) as signs of recent herniation. The internal herniations occurred at any time interval after the RYGB surgery.

Obstruction at the jejunojejunostomy all occurred within a year of the RYGB surgery, while incisional hernias occurred many years after open RYGB procedures. Patients suffering from intussusceptions all had an %EWL >100, while those suffering from incarcerated incisional hernias were significantly heavier with BMI >40 kg/m^2. Three patients each suffered from perforations in the gastroentero-anastomosis and in the jejunojejunostomy.

Other surgeries

The most common other surgery was cholecystectomy (n=23) for gallstone disease. Common bile duct stones were encountered in six patients (26%) and treated by laparoscopic common bile duct exploration in four patients, open choledochotomy in one patient, and left for spontaneous passage in another patient. The remaining surgeries were for small bowel obstruction (n=2), appendicitis (n=3), incarcerated incisional hernia (n=1), incarcerated epigastric hernia (n=1), ileal diverticulitis (n=1), and purulent peritonitis caused by salpingitis (n=1).

Unremarkable laparoscopies

Thirty patients underwent diagnostic laparoscopies without pathological findings. Twelve surgeries were prompted by pathological CT scans, while five patients had surgery without a prior CT scan.

Table 1. Patient characteristics, RYGB surgery information, and medical history for late admissions (>30 days) to the category of surgery performed.

		RYGB complication	Other surgeries	Diagnostic laparoscopy	No surgery performed	All patients	*p*-value
Patients n (%)		66 (25)	32 (11)	30 (11)	134 (51)	262	
Female n (%)		56 (85)	27 (84)	24 (80)	108 (81)	215 (82)	.527
Male n (%)		10 (15)	5 (16)	6 (20)	26 (19)	47 (18)	
Age at admission (years) Median (range)		39.2 (20-63)	41.5 (19-57)	33.3 (21-61)	39.4 (19-64)	39.1 (19-64)	.301
BMI at admission (kg/m²) Median (range)		27.4 (19-45)	29.1 (21-41)	28.7 (21-36)	28.7 (20-50)	28.4 (19-50)	.174
Missing, n (%)		*9 (14)*	*5 (16)*	*2 (7)*	*30 (22)*	*46 (18)*	
Time since RYGB (months) Median (range)		15.4 (1-95)	12.1 (1-87)	10.9 (2-65)	18.5 (1-162)	16.4 (1-162)	.429
Missing, n (%)		*5 (8)*	*4 (13)*	*3 (10)*	*18 (13)*	*30 (11)*	
RYGB surgery n (%)	Laparoscopic	61 (92)	29 (91)	125 (93)	243 (93)	28 (93)	n/a
	Open	5 (8)	3 (9)	6 (5)	16 (6)	2 (7)	
	Missing	*0*	*0*	*3 (2)*	*3 (1)*	*0*	
Status of mesenteric gaps n (%)	Closed at RYGB	28 (42)	18 (56)	58 (43)	123 (47)	19 (63)	n/a
	Closed later	2 (3)	0	14 (10)	22 (8)	4 (13)	
	Not closed	14 (21)	3 (9)	20 (15)	40 (15)	3 (10)	
	Unknown	22 (33)	11 (34)	40 (30)	77 (29)	4 (13)	
Chronic pain disease n (%)		7 (10)	3 (9)	3 (10)	15 (11)	28 (11)	n/a
CVD or hypertension n (%)		3 (5)	3 (9)	4 (13)	14 (10)	24 (9)	
Diabetes n (%)		1 (2)	0	0	4 (3)	5 (2)	
Pulmonary disease n (%)		6 (9)	1 (3)	0	8 (6)	15 (6)	

Continuous variables are presented as median (range) and categorical variables as frequency (percentage). -values are calculated using Kruskal-Wallis non-parametric test or Pearson's chi-square test. BMI = Body Mass Index, CVD = Cardiovascular disease.

Surgical complications

The majority of surgeries for RYGB complications were performed during on-call hours (35/66), while most diagnostic laparoscopies and cholecystectomies were performed during office hours (Table 3). Bariatric competency was only available for 12% (8/66) of surgeries for RYGB complications, but for 23% (7/30) of unremarkable diagnostic laparoscopies indicating that it was easier to find bariatric competency during office hours. The Clavien-Dindo classification showed relatively few complications with four patients requiring reoperations and hence classified as Clavien-Dindo III-IV. These patients had a significantly longer hospital stay of a median of 23 days (ρ <.001).

Discharge summary data

Aside from the 66 patients requiring surgery for RYGB complications, 37 patients were diagnosed with a biliary (gallstone) disease (23 operated and 14 non-operated). The largest group, however, were the 127 patients discharged with a diagnosis of unspecified abdominal pain (27 operated and 100 non-operated). The length of stay was a median of 3 days longer for those requiring operations and varied significantly between the different surgical categories, with surgery for intussusception and bowel perforations needing the longest hospital stay. (both ρ <.001). At discharge nine patients were planned for elective surgeries; four cholecystectomies, three mesenteric gaps closures, and two incisional hernia repairs.

Computed tomography

An unpublished subgroup analysis of the diagnostic accuracy of preoperative CT scans for diagnosing internal herniation in RYGB patients with acute abdominal pain was performed which resulted in a poster presentation at the Swedish Surgical week in Malmö in 2016. All patients with preoperative acute computed tomography scans that had subsequent abdominal surgeries were included. The diagnostic accuracy was very good with a sensitivity and specificity of 89% and 82% respectively. The positive and negative predictive values were 75% and 93% respectively (Figure 3).

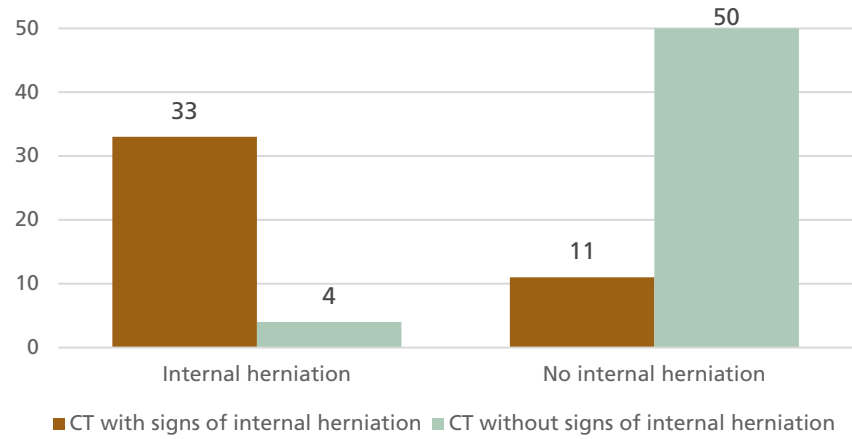


Figure 3. Bar chart of the diagnostic accuracy of CT in diagnosing internal herniation against findings at surgery.

Follow-up

The follow-up period was for a median of almost 5 years and recorded 267 readmissions by 113 patients. Three patients (1%) from the investigated cohort had died, but no hospital records were found to explain their cause of death. No deaths occurred during surgical admissions.

Readmission within 30 days was more common in those not operated at the first admission compared to those operated, although not statistically significant (13% vs. 6%, ρ =.052). Surgery for a RYGB complication continued to be the most common operation even during the follow-up, with 18 patients needing surgery for internal herniations. Recurrences had occurred in 4/42 (10%) patients that were operated for internal herniation. This was the same proportion as the number of patients discharged with unspecified abdominal pain that later suffered an internal herniation (11/127).

Moreover, patients with chronic pain disease were more likely to be readmitted both within 30 days, 7/32 (22%) vs. 19/248 (8%) (ρ =.009), and the full follow-up period, 20/32 (63%) vs. 93/248 (38%) (ρ =.007). However, they did not differ in terms of the need for surgery at readmission. Additional follow-up detail is available in Supplementary Table 1 (see Appendix, p.117).

Table 2. Admission data, preoperative diagnostics, and length of stay for late admissions (>30 days after RYGB).

		Surgery for RYGB complication						Other surgery					
		Internal herniation	Obstruction at jejunojejuno-stomy	Intussusception	Small bowel obstruction	Perforation	incisional hernia	Cholecystectomy	Miscellaneous	Unremarkable laparoscopy	All operated patients	All non-operated patients	*p*-values
Patients n (%)		42 (16)	4 (2)	2 (1)	9 (3)	6 (2)	3 (1)	23 (9)	9 (3)	30 (11)	128 (49)	134 (51)	
BMI at admission (kg/m²) Median (Range)		27.2 (19-39)	27.2 (26-41)	21.1 (19-23)	28.7 (21-35)	26.8 (20-33)	40.6 (37-45)	28.8 (21-41)	31.8 (24-36)	28.7 (21-36)	28.0 (19-45)	28.7 (20-50)	.274
Missing n (%)		*7 (17)*	*0*	*0*	*1 (11)*	*0*	*1 (33)*	*3 (13)*	*2 (22)*	*2 (7)*	*16 (13)*	*30 (22)*	
Time since RYGB (months) Median (Range)		15.4 (1-63)	4.2 (1-10)	12.5 (12-13)	16.9 (2-41)	19.3 (2-49)	83.7 (72-95)	11.3 (1-50)	25.2 (4-87)	10.9 (2-65)	14.1 (1-95)	18.5 (1-162)	.152
Missing n (%)		*3 (7)*	*0*	*0*	*1 (11)*	*0*	*1 (33)*	*3 (13)*	*1 (11)*	*3 (10)*	*12 (9)*	*18 (13)*	
Diagnostic investigation: n (%)													
CT scan		37 (85)	3 (75)	2 (100)	8 (89)	5 (83)	3(100)	9 (39)	5 (56)	26 (87)	98 (77)	94 (70)	.241
Ultrasound		3 (7)	0	0	0	0	0	14 (61)	1(11)	4 (13)	22 (17)	28 (21)	.445
MRCP		1 (2)	0	0	0	0	0	4 (17)	0	2 (7)	7 (6)	9 (7)	.673
Gastroscopy		2 (5)	0	0	1 (11)	0	0	0	1 (11)	7 (23)	11 (9)	9 (7)	.567
Preoperative status of mesenteric gaps n (%)	Closed	20 (48)	1 (25)	1 (50)	5 (56)	3 (50)	0	15 (65)	3 (33)	23 (77)	71 (56)	.908	
	Not closed	10 (24)	1 (25)	0	1 (11)	1 (17)	1 (33)	1 (4)	2 (22)	3 (10)	20 (16)	20 (15)	
	Unknown	12 (29)	2 (50)	1 (50)	3 (33)	2 (33)	2 (67)	7 (30)	4 (44)	4 (13)	37 (29)	40 (30)	
Length of hospital stay (days) Median (Range)		4 (2-24)	6 (5-8)	11 (5-17)	4 (2-19)	12 (6-21)	8 (5-34)	6 (3-22)	6 (3-9)	4.5 (1-26)	5 (1-34)	2 (1-16)	<.001

p-values are calculated using Mann-Whitney U non-parametric test or Pearson's chi-square test comparing operated to non-operated patients. BMI = Body Mass Index, CT = Computed Tomography, MRCP = Magnetic Resonance CholangioPancreatoagraphy

Table 3. Summary of variables for emergency surgery at late admissions (>30 days after RYGB) in relation to diagnosis at surgery.

		Surgery for RYGB complication						Other surgery			
		Internal herniation	Obstruction at jejunojejunostomy	Intussusception	Small bowel obstruction	Perforation	Incisional hernia	Biliary disease	Miscellaneous[1]	Unremarkable laparoscopy	All operated patients
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Patients		42 (16)	4 (2)	2 (1)	9 (3)	6 (2)	3 (1)	23 (9)	9 (3)	30 (11)	128 (49)
Bariatric surgeon		4 (10)	1 (25)	1 (50)	1 (11)	1 (17)	0	4 (17)	1 (11)	7 (23)	20 (16)
On call surgery		23 (55)	2 (50)	1 (50)	4 (44)	3 (50)	2 (67)	4 (17)	5 (56)	11 (37)	55 (43)
Method of surgical access:	Laparoscopic	27 (64)	3 (75)	0	5 (55)	1 (17)	1 (33)	21 (91)	4 (44)	28 (93)	90 (70)
	Converted	13 (31)	1 (25)	2 (100)	3 (33)	4 (67)	0	2 (9)	2 (22)	1 (3)	28 (22)
	Laparotomy	2 (5)	0	0	1 (11)	1 (17)	2 (67)	0	3 (33)	1 (3)	10 (8)
Open mesenteric gaps found at surgery		42 (100)	3 (75)	1 (50)	2 (22)	2 (33)	0	6 (26)	3 (33)	14 (47)	73 (58)
Clavien-Dindo classification of surgical complications	0	34 (81)	2 (50)	0	9 (100)	3 (50)	1 (33)	21 (91)	5 (56)	22 (73)	96 (75)
	I-II	6 (14)	2 (50)	2 (100)	0	3 (50)	1 (33)	0	4 (44)	7 (23)	26 (20)
	III-IV	1 (2)	0	0	0	0	1 (33)	2 (8)	0	0	4 (3)
	Missing	*1 (2)*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*1 (3)*	*2 (2)*

Categorical variables are rounded to the nearest whole number and presented as frequency (percentage).

Comments

This study showed that Roux-en-Y gastric bypass operated patients that were admitted for abdominal pain often suffered from a late surgical complication. Surgery for a RYGB complication was twice as common as other surgeries. The most common surgical complication was internal herniation (n=42) which seemed to occur at any time after the RYGB surgery and despite previously closed mesenteric gaps. The difficulty in diagnosing and ruling out RYGB complications was confirmed by the many patients that had negative explorative laparoscopies (n=30).

Obesity and weight loss following bariatric surgery increase the risk of gallstone formation. The second most common operation in this cohort was therefore a cholecystectomy (n=23), while another four patients were planned for elective cholecystectomies after discharge.

A large proportion of RYGB-operated patients suffered from unspecified abdominal pain. These patients also had a higher frequency of readmissions. This has been confirmed by several studies showing that up to 30% of RYGB-operated patients suffer from chronic pain and that hospital admissions increase after RYGB surgery.[152-155]

To the best of our knowledge, no previous study has reported the relative frequencies of diagnoses of acute surgical admissions of RYGB-operated patients from an acute surgical care perspective. Although this was a single-center study, we have no reason to believe that the relative frequencies would differ for other centers in Sweden. However, we anticipate that the number of internal herniations will decrease over time with the routine closures of the mesenteric gaps.

Paper II

Using the databases from Papers I and III, we retrieved 51 patients that had undergone surgery for acute internal herniation at Skåne University Hospital between April 2012 and December 2015. All patients had a history of laparoscopic RYGB. The female-to-male sex ratio among these patients was 4.5:1, which is a slight overrepresentation of females compared to the RYGB population as a whole. Internal herniations occurred at a wide time interval from the RYGB surgery, exemplified by the fact that one patient was admitted on the first postoperative day, while another presented 8 years after her RYGB operation (Table 4). More than half of the patients suffered an internal herniation despite having had primary closure of their mesenteric gaps at RYGB surgery.

Table 4. Demographics data of the RYGB patients with internal herniation (n=51).

Demographics:	**Median (min-max)**	**n**	**(%)**
Sex			
Female		42	(82)
Male		9	(18)
Age (years)	38.8 (20-58)		
BMI (kg/m^2)	26.5 (19-39)		
Missing data		5	(10)
% Total weight loss	34.6 (8-55)		
Missing data		14	(27)
Data from RYGB surgery:			
Time since surgery (months)	21.2 (0-96)		
Primary closure of mesenteric gaps:			
Closed		26	(51)
Not closed		12	(23.5)
Unknown		13	(25.5)

Internal herniation surgery

Surgeons with competency in bariatric surgery operated on six patients, while the remaining patients were operated on by acute care surgeons. Three surgeries were planned laparotomies, while the rest were attempted laparoscopically. Both bariatric surgeons and acute care surgeons had a conversion rate of 33%. (Table 5) Patients that had laparoscopic surgery had a shorter hospital stay of a median of two days compared to four days for those requiring open surgery (ρ <.001). Internal herniations occurred with a similar frequency in Petersen's space (n=27) and beneath the jejunojejunostomy (n=24). The mesenteric gaps were normally closed with running braided non-bio-absorbable sutures, e.g. Ethibond Excel™ (Ethicon Inc., Johnson & Johnson, Tokyo, Japan).

Table 5. Results of internal herniation surgery

	n	%
Method of surgical access:		
Laparoscopic	32	63
Converted	16	31
Laparotomy	3	6
Surgical competency:		
Acute care surgeon	45	90
Bariatric surgeon	6	10
Internal herniation in:		
Petersen's space	27	53
Beneath jejunojejunostomy:	24	47

Follow-up

The median follow-up of the patients was 74.4 months. One patient was lost to follow-up for having moved abroad. (Table 6) Unfortunately, no information was available on when the patient moved abroad, so this patient was excluded from the analysis. During follow-up more than half of the patients (52%) had repeat emergency room visits and just over one-third (36%) needed one or more readmission(s) at surgical wards. Four patients required surgery for common surgical diagnosis; two cholecystectomies, one appendectomy, and one sigmoid resection for volvulus.

Six patients suffered a recurrence of internal herniation after a median of 30 months from the first occurrence. These first recurrences occurred after surgeries by acute care surgeons, and all occurred at the other mesenteric gap. Two patients suffered one and two additional recurrences respectively, all in Petersen's space.

The total number of abdominal CT scans was 86, with 40 CT scans being performed on just three patients. Two of these patients had more than 20 ER visits and 10 and 15 readmissions respectively for chronic abdominal pain. Neither of them suffered a recurrence of internal herniation. However, one patient had surgery twice for small bowel intussusception and once an explorative laparotomy without any significant findings, while the other patient underwent three diagnostic laparoscopies with an eventual revision of their jejunojejunostomy. These were all considered RYGB-related complications. One additional patient had surgery for small bowel obstruction caused by adhesions after the RYGB operation.

Table 6. Follow-up data for patients operated for internal herniation by type of surgeon.

	Bariatric surgeon		**Acute care surgeon**		**All**	
Patients observed (n)	5		45		50	
Lost to follow-up	1		0		1	
Median follow-up (months)	68.5 (49-87)		74.8 (48-92)		74.4 (48-92)	
Time to 1st readmission (months)	6.2		14.1 (0.1-50)		8.8 (0.1-50)	
Time to IH recurrence (months)	n/a		30 (2.5-65)		30 (2.5-65)	
Patients having:	*n*	(%)	*n*	(%)	*n*	(%)
1 CT scan	1	(25)	5	(11)	6	(12)
2 CT scans	0	0	6	(13)	6	(12)
>3 CT scans	1	(25)	8	(18)	9	(18)
ER visit(s)	1	(25)	25	(56)	26	(52)
Readmission(s)	1	(25)	17	(38)	18	(36)
Surgery for:						
recurrent IH:			6	(13)	6	(12)
- in Petersen's space:	0		4	(9)	4	(8)
- beneath jejunojejunostomy:			2	(4)	2	(4)
multiple IH recurrences	0		2	(4)	2	(4)
other RYGB complication	1	(20)	2	(4)	3	(6)
other acute abdominal condition	0		4	(9)	4	(8)

The data is presented as count (column percentages) or median (minimum-maximum).

Figure 4 illustrates the cumulative fraction of patients that were readmitted or had a recurrence of internal herniation during follow-up. The figure clearly illustrates that roughly a third of all readmissions were caused by a recurrent internal herniation and that they are evenly spread over time.

Comments

This study highlights several important points about internal herniations. The study reiterates the fact that primary internal herniations as well as recurrences of internal herniations may occur at any time after RYGB surgery.[94] Patients suffering from internal herniations continue to constitute a large proportion of the RYGB patients admitted for acute abdominal pain. This is because internal herniation is the most common RYGB complication, even after the closure of the mesenteric gaps. The recurrence rate of 12% is lower than previously published, however, it is higher than the reported risk of primary internal herniations. [81,86,94]

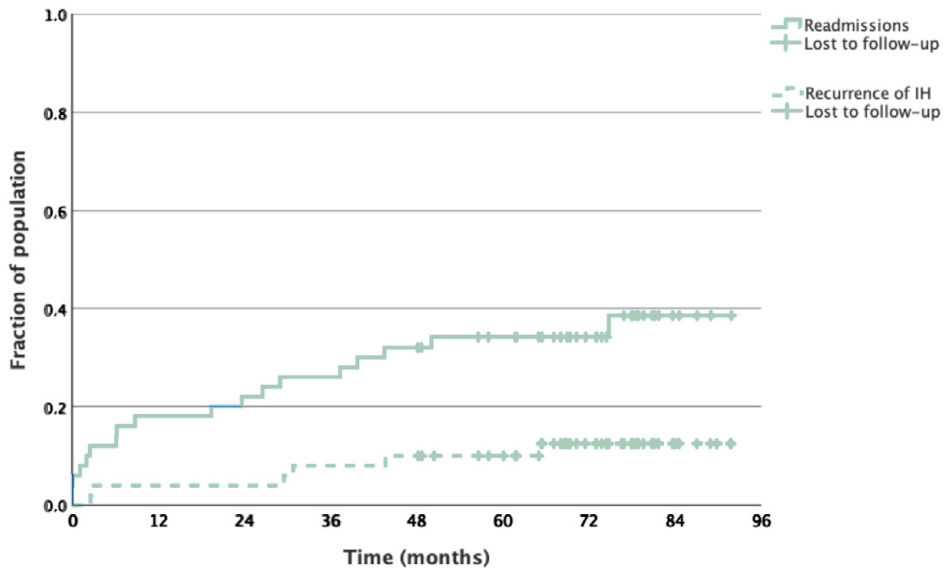


Figure 4. Kaplan-Meier curve of the fraction of the study cohort with readmissions and recurrences of internal herniation (IH) during follow-up.

Furthermore, the study showed that all first recurrences occurred in the non-treated mesenteric gap, suggesting that both mesenteric gaps need to be thoroughly investigated and any visible gaps or weaknesses need to be strengthened and closed to reduce the risk of recurrence further. In this cohort, bariatric surgeons were better at ensuring that both the mesenteric gaps were adequately closed, since patients operated by bariatric surgeons did not suffer any recurrences.

The frequency of CT scans performed during follow-up was 48% and this was higher than the 40% previously reported by Sandvik et al. for a longer follow-up and may signify a general trend toward a lower threshold and higher usage of imaging in

emergency departments.[156] The large proportion of patients needing ER visits and readmissions is unfortunately a well-known problem of RYGB.[152-153] The two patients diagnosed with chronic pain were fewer than reported in other studies, but they continue to constitute a great diagnostic and therapeutic challenge.[154-155]

Paper III

Patients were included prospectively, from June 2015 to December 2017, resulting in identification of 46 patients which met the inclusion criteria. Chart review found that eight patients required surgery for internal herniation, five patients for small bowel obstruction of another cause, twelve patients received another specified diagnosis at discharge, while 21 patients were discharged without a specified diagnosis for their acute abdominal pain (Figure 5).

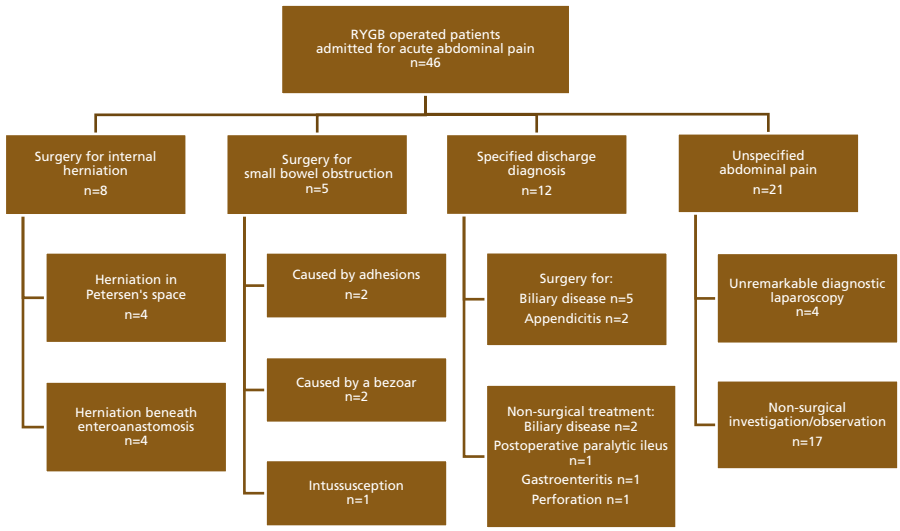


Figure 5. Flow chart of study cohort with categorization into diagnosis groups and outcome.

The study cohort demographics showed no significant differences between the groups in terms of age (ρ =.204) or BMI (ρ =.627). The female-to-male sex ratio among these patients was slightly less than 3:1, which is a slight underrepresentation of females compared to those undergoing RYGB surgery, where the ratio is above 3:1 (Table 7). Patients reported few comorbidities, however, almost one-third (30%) stated that they suffered from a chronic pain disease and almost half (46%) wrote that they suffered from a psychiatric disorder and/or substance abuse, which is more than expected.

The eight internal herniations were equally distributed in Petersen's space and beneath the jejunojejunostomy. No surgery reported ischemic bowels and no bowel resections were performed. Five patients had surgery for small bowel obstructions that were caused by adhesions (n=2), bezoars impacted in jejunojejunostomy (n=2), or a long intussusception (n=1). Among patients with other specified diagnoses, five underwent cholecystectomies, two underwent appendectomies and five patients were treated conservatively. Four out of 21 patients were discharged with a diagnosis of unspecified abdominal pain and had undergone unremarkable exploratory laparoscopies.

The duration of hospital stay varied significantly between the groups (ρ =.002) and also between operated (median of 5 days) and non-operated (median of 3 days) patients (ρ <.001). Only three readmissions occurred among patients discharged without an explanation for their abdominal pain. One patient underwent an unremarkable diagnostic laparoscopy, but all three patients were again discharged with the diagnosis of unspecified abdominal pain. Furthermore, no occurrence of internal herniation was noted during an extended 3-year follow-up of this subgroup.

Table 7. Study cohort's demographics, comorbidities, and admission data.

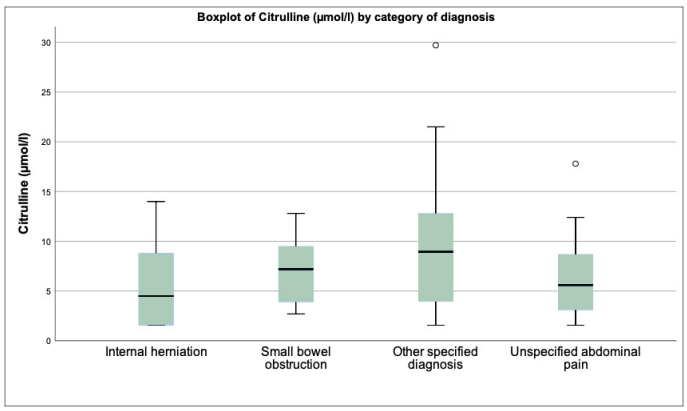
	Internal herniation	Small bowel obstruction	Other specified diagnosis	Unspecified abdominal pain	All
Patients	8	5	12	21	46
Age, y	50 (30-72)	46 (32-50)	48 (22-59)	41 (24-63)	46 (22-72)
Sex male	2 (25%)	0	7 (58%)	3 (14%)	12 (26%)
female	6 (75%)	5 (100%)	5 (42%)	18 (86%)	34 (74%)
BMI (kg/m^2)	29 (24-32)	25 (20-42)	31 (24-40)	29 (18-46)	29 (18-46)
Cardiovascular disease	2 (25%)	0	3 (25%)	4 (19%)	9 (20%)
Diabetes	1 (13%)	0	1 (8%)	1 (5%)	3 (7%)
Pulmonary disease	1 (13%)	0	3 (25%)	2 (10%)	6 (13%)
Chronic pain disease	1 (13%)	1 (20%)	6 (50%)	6 (29%)	14 (30%)
Psychiatric disease	4 (50%)	0	4 (33%)	13 (62%)	21 (46%)
Abdominal CT scan	7 (88%)	5 (100%)	8 (67%)	15 (71%)	35 (76%)
Operated	8 (100%)	5 (100%)	7 (58%)	4 (19%)	24 (52%)
Time to surgery (hours)	24.5 (11-112)	10 (5-181)	26 (14-107)	61.5 (20-132)	25 (5-132)
Hospital stay (days)	4 (3-19)	6 (4-16)	5 (2-22)	3 (1-22)	4 (1-22)
Readmission <30 days	0	0	0	14% (3)	7% (3)

Values are presented as a median (minimum-maximum) or as count (percentages).

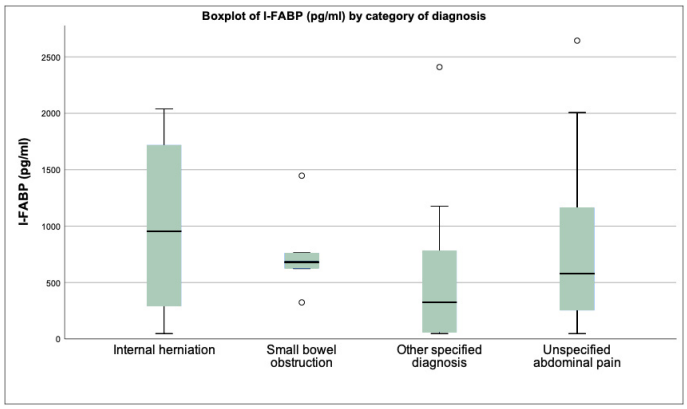
Biomarkers

None of the investigated biomarkers showed any significant differences between the groups as demonstrated in the boxplots in Figure 6 (a-f). When specifically comparing the biomarkers for diagnosing internal herniation it was revealed that significantly lower lactate levels (ρ=.029) and borderline lower D-dimer levels (ρ=.053) were associated in patients with internal herniation. Overall, no routine biomarker was elevated in patients with internal herniations, as most white blood cell (WBC) counts and D-dimer values were normal, and all CRP levels were normal (<3.5 mg/l).

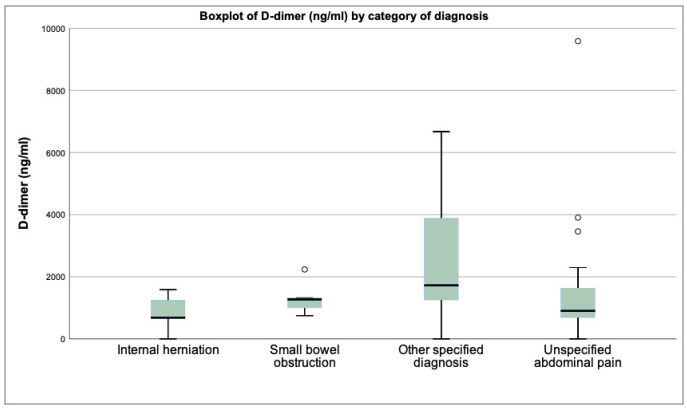
a) Citrulline (µmol/l)



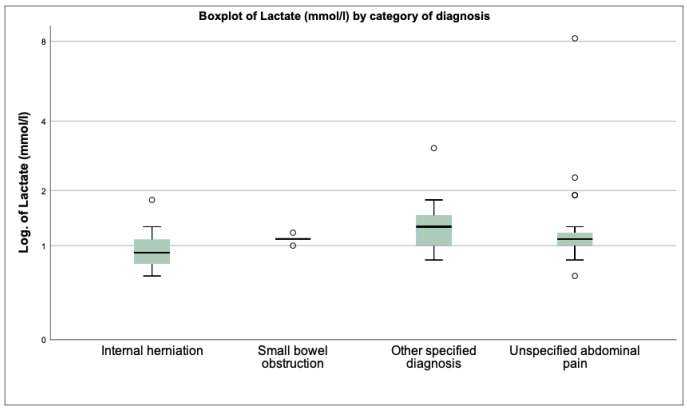
b) Intestinal-Fattyacid binding protein (I-FABP) (pg/ml)



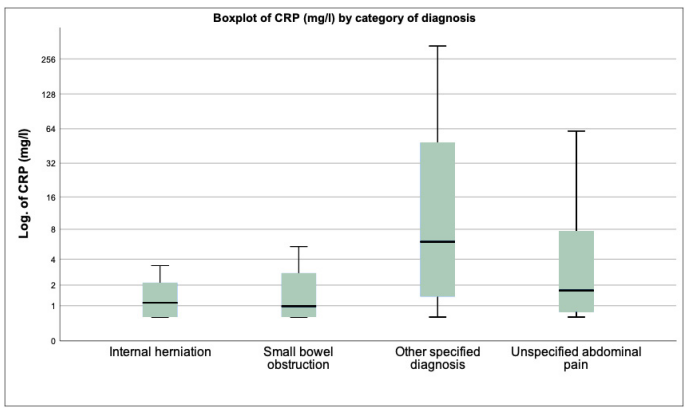
c) D-dimer (ng/ml)



d) Lactate (mmol/l)



e) C-reactive protein (CRP) (mg/l)



f) White blood cell (WBC) count (10^9/l)

Figure 6.a-f. (a) Citrulline (µmol/l), (b) I-FABP (pg/ml), (c) D-dimer (ng/ml), (d) Lactate (mmol/l), (e) CRP (mg/l) concentrations and (f) WBC count (109/l) by the diagnosis category. Outliers are indicated with °.

Pain questionnaire

Patients reported consistently high levels of pain, both at pain onset and at admission, with no significant difference between the groups (Table 8). It was noted, however, that patients with small bowel obstructions of other causes than internal herniation more often had milder pain at the onset that increased until presentation at the hospital. No significant difference in time from pain onset to admission was seen between the groups or for patients with internal herniation compared to the rest.

Table 8. Pain questionnaire results by the diagnosis category.

	Internal herniation	Small bowel obstruction	Other specified diagnosis	Unspecified abdominal pain	All	ρ-values
Total:	8	5	12	21	46	
Pain level: Numerical Rating Scale (1-10)						
at symptom onset	9 (7-10)	5 (3.5-7.5)	8.5 (6-9.75)	9 (5-10)	9 (5-10)	.510
at presentation	9 (8-10)	10 (8.5-10)	8.5 (6-10)	10 (9-10)	9 (8-10)	.454
Time from pain onset to admission (hours)	13 (8-121)	26 (24-47)	31 (19-126)	25 (20-52)	25.5 (28-68)	.870
Missing data (*n*)	1	0	4	2	7	

Values are presented as a median (interquartile range). ρ values were calculated using the Kruskal-Wallis test.

Comments

In conclusion, none of the investigated biomarkers showed any promise of being used in the diagnosis of internal herniation. This is probably because the intestines, during the early stages of incarceration, have not yet had the affected or damaged mucosa required to induce any biochemical ischemic changes. This theory was confirmed in the clinical setting, as none of the operated patients had bowels with ischemic changes at the surgery. Ideally, a biomarker needs to be able to diagnose patients before ischemic changes occur, making these results somewhat disappointing albeit interesting.

Since most patients with internal herniation present with normal laboratory results, any elevated laboratory tests will, therefore, make it less likely that the patient has an internal herniation. With elevated laboratory tests, inflammatory disease is more likely compared to a bowel obstruction. Furthermore, no differences in the duration or level of pain were observed between the diagnoses, suggesting that a simple assessment of pain level or duration is not very helpful in determining the differential diagnosis. In the clinical setting, more detailed history-taking would, however, still play a significant role.

Paper IV

The database search for acute computed tomography (CT) scans of RYGB-operated patients with mention of intussusception in the report during 2012-2019 retrieved 73 scans. We excluded one patient that had a reversal of her gastric bypass and 37 patients with negative CT findings. The remaining 35 CT scans were available for analysis. After chart review, these were subdivided into the following categories: acute intussusception, intermittent intussusception, and incidental intussusception (see p. 53 in Materials and Methods). The inclusion and outcome of the patient cohort are presented in Figure 7.

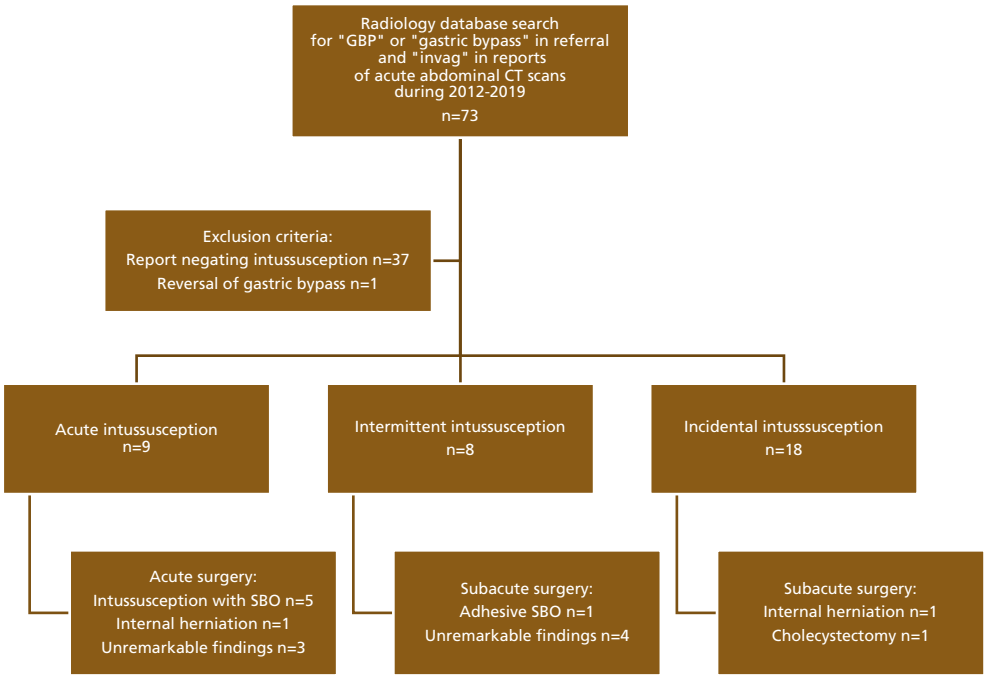


Figure 7. Flow chart of inclusion and outcome of the patient cohort.

Acute intussusception

Nine patients were categorized as acute intussusception as they had a serious clinical presentation demanding emergency surgery within 24 hours. One patient presented with peritonitis while the others had opiate-resistant pain. The acute surgeries found persistent intussusceptions in five patients. All of them needed active reduction, while three patients had ischemic strangulated intussusceptions involving the jejunojejunostomy, two of which also had perforations. All ischemic bowels needed resection and reconstruction of the anastomosis. Two other patients had viable jejunal intussusceptions causing an obstruction which were handled with reduction without resection. One patient had a CT scan finding of a 160mm long intussusception which was successfully reduced laparoscopically (Figure 8). Another patient required an open reduction of intussuscepted bowel that had become ischemic (Figure 9).

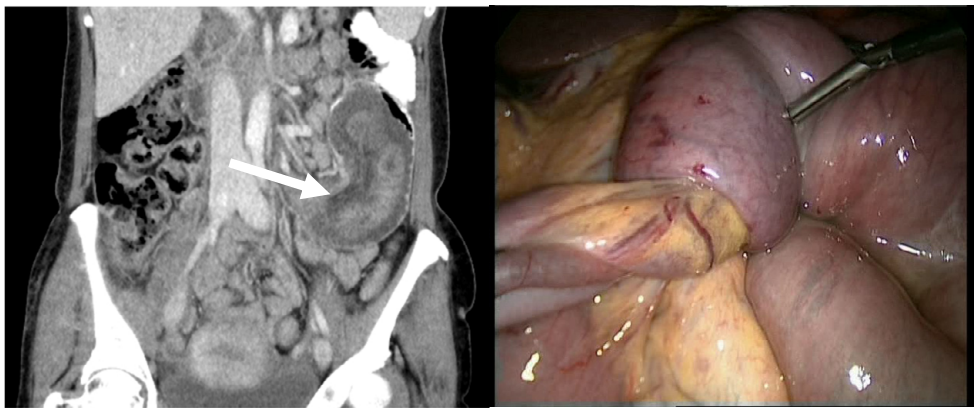


Figure 8. Left: CT illustrating a 160mm long jejunal intussusception (white arrow). Right: Laparoscopic reduction of intussusception in process.(Picture courtesy of Mikael Ekelund)

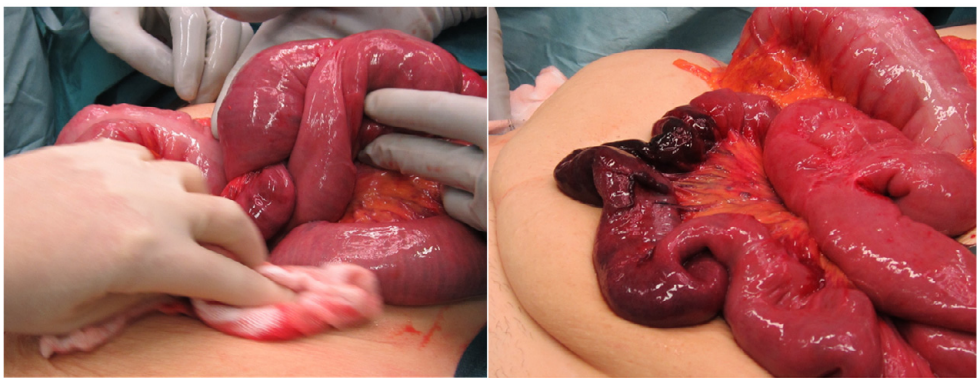


Figure 9. Open surgery for acute intussusception.
Surgery of a retrograde intussusception invaginated into the jejunujejunostomy in the process of being reduced (left). Ischemic bowel after reduction (right).

Out of the remaining four patients, one patient had an unexpected internal herniation diagnosed at surgery, while the other three patients had unremarkable findings. Two patients had preventive measures to reduce the risk of recurrence as it was determined that the intussusception must have caused the patients' symptoms although it had resolved spontaneously. One patient had an enteropexy, while the other patient had a resection of an enlarged biliary blind end at the jejunojejunostomy without reconstruction of the actual anastomosis. The third patient with unremarkable findings only had closure of open mesenteric defects as per the routine at the time.

Intermittent intussusception

Eight patients were given intussusception as the cause of their abdominal pain at discharge from the hospital. Four patients underwent unremarkable laparoscopies, but for two patients the surgeons decided to reconstruct the jejunojejunostomy to an isoperistaltic side-to-side anastomosis as a preventive measure to reduce the risk of recurrence of intussusception. A fifth patient had a laparotomy for adhesive small bowel obstruction. This patient had already had an elective revision of her jejunujejunostomy a year prior to this event. Three other patients did not undergo any explorative surgery but were discharged when symptoms subsided and were planned for outpatient follow-up. One of these patients had an elective reconstruction of her jejunujejunostomy four months before admission.

Incidental intussusception

The intussusceptions were treated as incidental findings in more than half of the patients (18/35). Six patients were not admitted for observation. Twelve patients were admitted and treated for other surgical diagnoses or received a diagnosis of unspecified abdominal pain at the discharge without reference to the intussusception. Two patients underwent subacute surgery for an internal herniation and a subacute cholecystectomy following biliary pancreatitis respectively.

Patient outcome

The study cohort was investigated by comparing the above-mentioned groups, but more importantly by analyzing the five intussusceptions causing bowel obstruction needing acute reduction at the surgery. There was no difference in age (ρ=.223), BMI (ρ=.099), or time since RYGB surgery (ρ=.792) between the groups (Table 9). Comparing the five patients with intussusceptions causing SBOs against the rest of the cohort did not find any significant differences in terms of age (ρ=.069), BMI (ρ=.071), or time since RYGB surgery (ρ=.873). No significant differences between the groups were observed in terms of presenting symptoms. In the cohort as a whole 37% had chronic pain, 45% had nausea, and 31% had vomiting at presentation. Hospital stay was significantly different between the groups (ρ=.004), but only significantly different for patients with intussusceptions causing SBO compared to the rest when an outlier with 63 days stay for chronic pain was excluded from the analysis (ρ=.039).

Table 9. Study cohorts' demographics, presentation symptoms, and admission data are categorized by the clinical category or for bowel obstruction.

	Intussusception				
	Acute	Intermittent	Incidental	Causing bowel obstruction	Not causing bowel obstruction
Total	9	8	18	5	30
Sex					
Female	9	7	15	5	26
Male	0	1	3	0	4
Age (years)	41.3 (23-57)	34.7 (20-47)	38.2 (28-52)	41.3 (36-55)	35.9 (20-57)
BMI (kg/m^2)	24.0 (19-27)	27.2 (22-41)	26.5 (21-33)	23.0 (19-27)	25.6 (21-41)
Missing data	0	0	4	0	6
Time since RYGB (months)	32.4 (5-81)	25.1 (10-79)	30.0 (5-107)	32.4 (12-81)	26.6 (5-107)
Missing data	0	0	0	0	0
Symptoms:					
Acute abdominal pain	9	8	18	5	30
Chronic pain	4	4	5	2	11
Vomiting	4	2	5	3	8
Nausea	7	5	12	4	12
Hospital stay (days)	7 (2-17)	6.5 (3-63)	2.5 (2-6)*	9 (3-17)	3.5 (2-63)*
(Re)admission					
Within 30 days	2	1	2	1	4
Within 1 year	4	5	2	2	9
Intussusception recurrence					
Within 30 days	0	0	0	0	0
Within 1 year	1	1	0	0	2

Data is presented as count (n) or median (minimum-maximum) as appropriate. * Excluding six patients that were not admitted.

In summary, 7/14 (50%) of patients that underwent surgery showed unremarkable findings, while only five patients had intussusceptions requiring emergent surgery for being incarcerated. Four patients underwent procedures to prevent a recurrence and remained free from recurrence at a one-year follow-up. Two patients that underwent unremarkable laparoscopies had recurrences of intussusceptions within a year. Both patients underwent reconstruction of their jejunojejunostomy at readmission. Patients categorized with incidental intussusception did not have any recurrences within a year.

Radiological reevaluation

Both radiologists considered the 35 CT scans sufficient in quality. Intravenous contrast enhancement was used for all acquisitions, while three patients did not have any additional positive oral contrast. One radiologist diagnosed a suspected internal herniation instead of intussusception for one scan, while the other radiologist also did

not verify an intussusception for one scan. These patients did not undergo surgery and did not suffer any recurrent intussusception within a year.

The reexamination protocol (Table 10) compared patients with intussusception causing SBO to intussusceptions not causing SBO for the 34 evaluated scans for each radiologist. The analysis showed that most intussusceptions were located in the LUQ without any difference between the groups. Positive oral contrast was often skipped in the most emergent scans, thereby not allowing for an evaluation of the passage of oral contrast.

Table 10. Results of radiological reexamination of acute abdominal CT scans reporting an intussusception.

	Radiologist O.E.			Radiologist D.L.		
	Intussusception			Intussusception		
	Causing bowel obstrution	Not causing bowel obstruction	ρ-value	Causing bowel obstruction	Not causing bowel obstruction	ρ-value
CT scans	5	29		5	29	
Length of intussusception (mm)	113 (30-160)	42 (18-110)	.014[b]	160 (115-220)	30 (14-240)	<.001[b]
Long (>100mm)	4	2	.0015[a]	5	4	.0005[a]
Short (≤100mm)	1	27		0	25	
Located in the left upper quadrant?	3	20	1.0[a]	3	25	.205[a]
Proximal bowel dilatation?	5	5	<.001[a]	5	12	.044[a]
Passage of oral contrast?	1[†]	29	.065[a]	0[†]	22	.077[a]
Signs of internal herniation?	0	0	n/a	0	2	n/a

Data is presented as count (n) or median (minimum–maximum). [a]Fisher's Exact test, [b]Mann-Whitney U test. [†]Three patients were not administered any oral contrast. LUQ = Left Upper Quadrant.

Proximal bowel dilatation significantly correlated to intussusception with SBO for both radiologists O.E. and D.L. (ρ=.001 and ρ=.044), with the more experienced radiologist O.E. using this definition more precisely and selectively. It also correlated to all SBO, when combining patients with internal herniation and adhesive SBO (ρ=.041 and ρ=.035).

Intussusception length as measured on CT by each radiologists, plotted in Figures 10 and 11, was significantly longer for patients with intussusceptions causing SBO (ρ=.014 and ρ<.001). Using a suggested threshold for intussusception length of 100 mm to differentiate intussusceptions causing SBO gave a high sensitivity and specificity of 80% and 93% for radiologist O.E. and 100% and 86% for radiologist D.L. respectively (Table 10) The positive and the negative predictive values were 67% and 96% for radiologist O.E. and 56% and 100% for radiologist D.L. respectively.

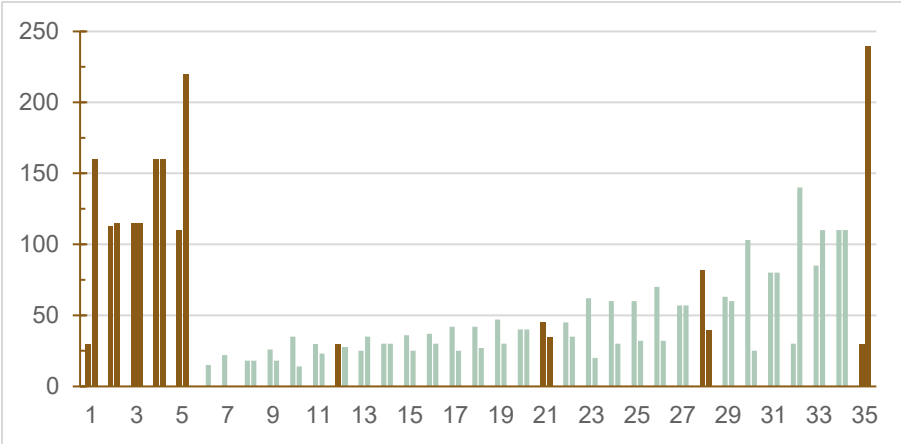


Figure 10. A bar chart of the intussusception length on CT in millimeters by radiologists O.E. and D.L. displayed in order of incremental size. Acute surgeries are marked in brown and the five patients with bowel obstruction are presented first (1-5).

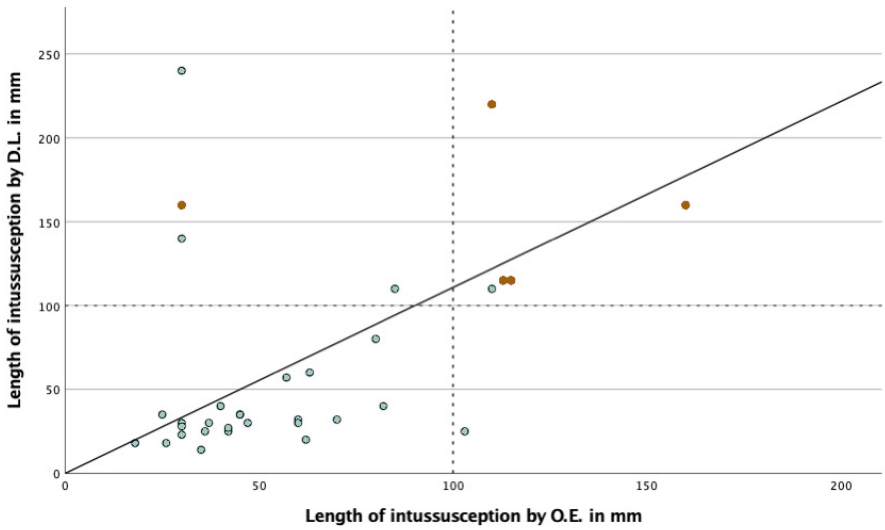


Figure 11. Scatter plot of intussusception length by D.L. against intussusception length by O.E. Scans of patients with intussusceptions causing bowel obstructions are marked in brown. A best-fit line was added, as well as dotted lines indicating the proposed 100mm threshold.

The radiologists' measurements showed a moderate correlation with Spearman's rho ρ= .429. The 100mm threshold for intussusception length also showed a moderate correlation in inter-rater reliability with Cohen's kappa of κ=.574.

Comments

The novel findings of this study provide new and encouraging knowledge that may help guide clinicians in their decision-making process. For example, a CT finding of a short intussusception can be considered an incidental finding and the asymptomatic patient can be reassured. On the other hand, a long intussusception indicates potential bowel obstruction and may alert the surgeon of the need for urgent surgery. The clinical relevance of intussusception length has only previously been described in children by Wu et al., where they showed that long intussusceptions increased the likelihood of bowel resection.[157]

Paper V

The cross-matching of the national registries SOReg and GallRiks retrieved 550 records of Roux-en-Y gastric bypass-operated patients undergoing cholecystectomies with intraoperative cholangiography finding of common bile duct stones. Out of these, 145 patients were treated by intraoperative endoscopic retrograde cholangiography (ERC) and 132 patients were treated by laparoscopic transcystic common bile duct exploration (LTCBDE) and hence included in this comparative study (Figure 12). Other management techniques included laparoscopic (n=18) or open choledochotomy (n=58) or preparation for a postoperative ERC (n=14). The CBD stones in a quarter of the patients were simply flushed out with saline (n=143), while those of less than a tenth of the patients were left without intervention (n=38) perhaps expecting a spontaneous passage.

The studied procedures (n=277) were reported from 47 hospitals (1-24 procedures/hospital), with 23 hospitals reporting fewer than five procedures. The study cohort showed no significant differences in BMI, sex, or ASA score (American Society of Anesthesiologists) between the two compared treatment modalities (Table 11). Patients undergoing ERC were slightly heavier than those undergoing LTCBDE but the results were only borderline significant (ρ=.052) and 22-30% of data for this variable were missing.

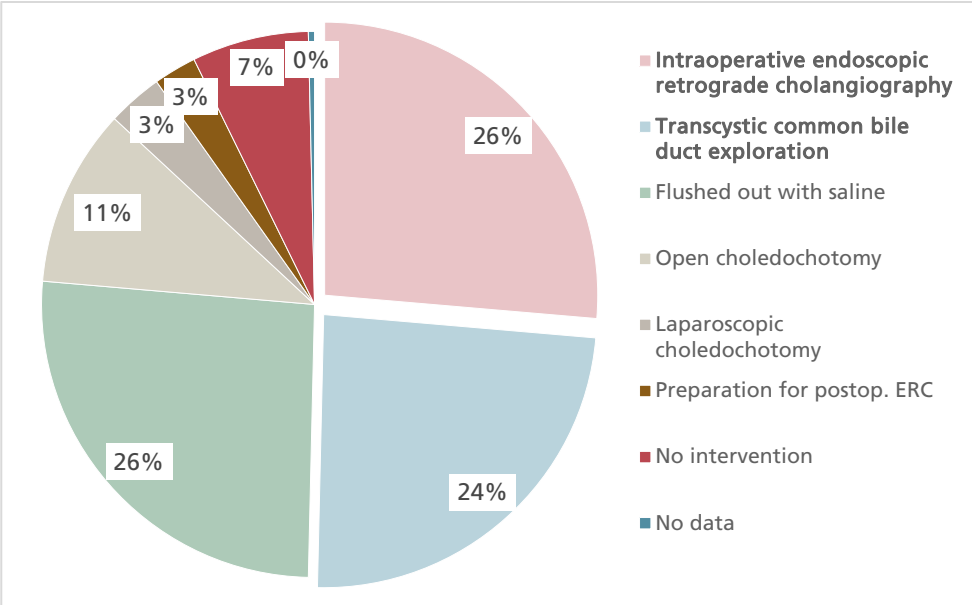


Figure 12. Pie chart of reported management techniques for RYGB patients with an intraoperative finding of common bile duct stones during cholecystectomy.

Table 11. Demographics and ASA score of the study cohort

	Transcystic common bile duct exploration	Intraoperative endoscopic retrograde cholangiography	*p* -values
	n=132	n=145	
Age (years)	46 (19-69)	47 (19-74)	.518[b]
BMI (kg/m2) *Missing*	28.9 (17.8-48.4) 29 (22%)	30.8 (20.0-45.2) 43 (30%)	.052[b]
Sex			
Female Male	110 (83%) 22 (17%)	120 (83%) 25 (17%)	.899[a]
ASA score			
I II III	38 (29%) 76 (58%) 18 (13%)	37 (26%) 87 (60%) 21 (14%)	.377[a]

Numbers are presented as count (percentage), while age and BMI are presented as median (min-max). [a] Pearson's chi-squared test, [b] Mann Whitney U non-parametric test

Both studied procedures, LTCBDE and ERC were more often performed in the acute setting, where ERC was significantly overrepresented (63% vs. 78%, ρ=.006, Table 12). Elevated bilirubin or icterus as a preoperative indication of cholestasis was also more common in the ERC group compared to the LTCBDE group (64% vs. 45%, ρ=.002). Interestingly, CBD stones were encountered in 45% of patients that did not have a preoperative suspicion.

There were a few differences between the techniques. Intraoperative ERC was utilized for significantly larger stones with the distribution of stone sizes illustrated in Figure 13 (ρ<.001). The total procedure time including the cholecystectomy was significantly shorter for LTCBDE, being on average 31 min faster, 95% CI [10.3-52.6] (ρ=.005, Figure 14). Patients undergoing LTCBDE also had a statistically significantly shorter postoperative stay (ρ=.041), although the real difference was small with a median of two days for both procedures.

Adverse events

The data only reported one intra-operative adverse event in the LTCBDE group and three adverse events in the ERC group, which are too few to show a statistical difference. One of the adverse events in the ERC group was an intestinal perforation. From the data, we could not determine whether this was a consequence of the cholecystectomy or the ERC procedure. Postoperative adverse events occurred in about one in six patients with little difference between the two procedures (Table 12). Postoperative abscesses were more frequent after ERC, probably as a result of the gastrotomy, while remaining CBD stones were encountered more often after LTCBDE, although the results remained insignificant (Table 12).

Table 12. Outcome comparison between transcystic common bile duct exploration and intraoperative ERC.

	Transcystic common bile duct exploration	Intraoperative endoscopic retrograde cholangiography	ρ-values
Procedures	132	145	
Hospitals	33	33	
Hospitals >5 procedures	10	9	
Preoperative data			
Elevated bilirubin	60 (45%)	93 (64%)	.002 [a]
Acute cholecystitis	29 (22%)	46 (32%)	.068 [a]
Acute pancreatitis	11 (9%)	11 (8%)	.818 [a]
Surgical data			
Acute surgery	83 (63%)	113 (78%)	.006 [a]
Surgery time (min)	159 (47-415)	200 (40-480)	.005 [c]
Completed laparoscopically	114 (86%)	129 (89%)	.510 [a]
Size of largest CBD stone:			
> 8 mm	11 (8%)	36 (25%)	
4 - 8 mm	82 (62%)	85 (58%)	<.001 [a]
< 4 mm	39 (30%)	24 (17%)	
Intra-operative adverse events	1 (1%)	3 (2%)	.624 [b]
Postoperative length of stay (days)	2 (0-27)	2 (0-35)	.041 [c]
Postoperative data (30 days)	130 (98%)	140 (97%)	
Postoperative adverse events	21 (16%)	25 (18%)	.710 [a]
Abscess	1 (1%)	6 (4%)	.122 [b]
Bleeding	4 (3%)	3 (2%)	.714 [b]
Bile leak	3 (2%)	3 (2%)	1.0 [b]
Bowel perforation	1 (1%)	1 (1%)	1.0 [b]
Remaining stone	2 (2%)	0	.230 [b]
Cholangitis	2 (2%)	0	.230 [b]
Additional ERC	2 (2%)	2 (2%)	1.0 [b]
Reoperation	2 (2%)	3 (2%)	1.0 [b]

Numbers are presented as count (percentage), while time is presented as median (min - max). CBD = common bile duct. ERC = Endoscopic retrograde cholangiography.

[a] Pearson's chi-squared test, [b] Fisher's Exact test, [c] Mann Whitney U non-parametric test

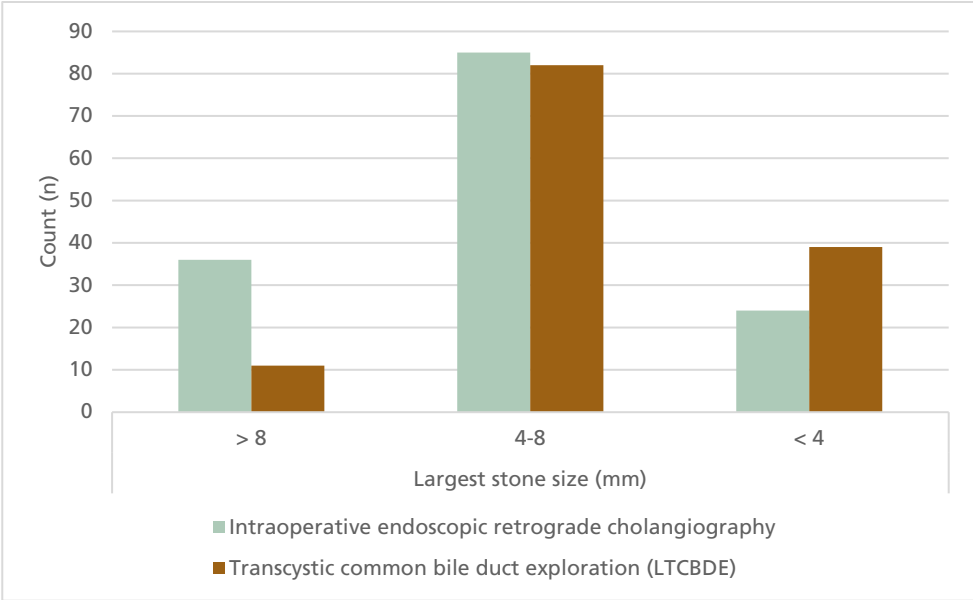


Figure 13. Bar chart of the largest common bile duct stone size in millimeters for each procedure.

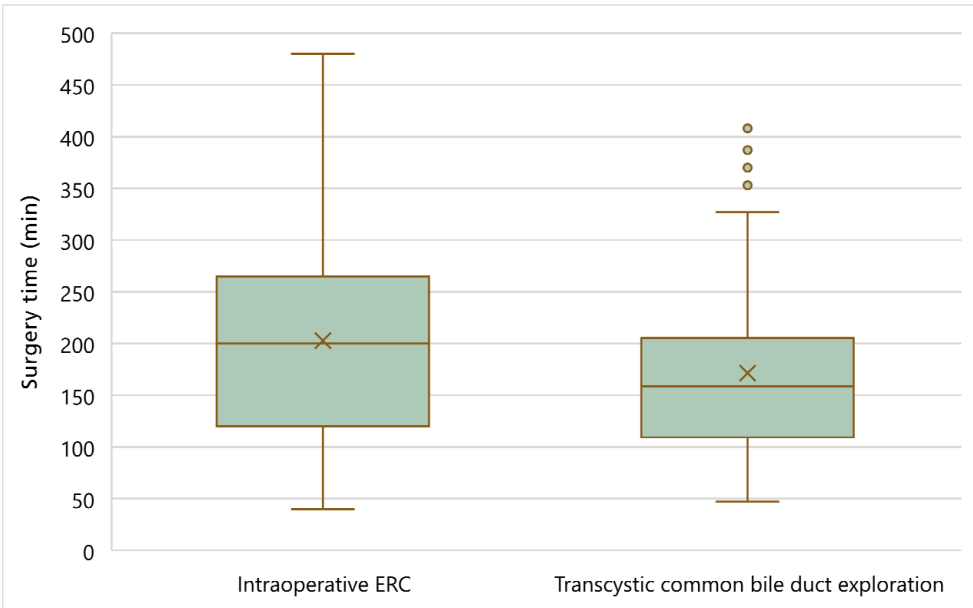


Figure 14. Boxplot of operating time of cholecystectomies with intraoperative ERC or laparoscopic transcystic common bile duct exploration for treatment of common bile duct stones in RYGB patients. The "X" shows the mean time.

Comments

In light of the complexity of clearing CBD stones in post-RYGB patients, it is important to remember that studies have shown that spontaneous passage of asymptomatic CBD stones cannot be predicted by the number or size of stones, or by the diameter of the bile duct.[135,158] Additionally, it is not possible to anticipate which patients will experience complications related to residual stones. Such complications may be biliary colic, jaundice, or pancreatitis, which may be severe or potentially fatal. Because of the complexity of managing CBD stones in post-RYGB patients and the potentially severe consequences of any residual stones an attempt to achieve stone clearance intraoperatively should be the recommended practice in the post-RYGB patient.

In the present study, intraoperative cholangiography was routinely performed in all cholecystectomies, which may not be the case in all settings. Considering that CBD stones were observed in 45% of patients without a preoperative suspicion, an intraoperative cholangiogram is probably advisable for post-RYGB cholecystectomies.

The study found that both examined procedures to clear common bile duct stones in Roux-en-Y gastric bypass patients showed comparable results with few complications. The main difference was related to the size of extracted CBD stones. While ERC was more often used in larger stones, consequently LTCBDE was more common for smaller stones. There may be several explanations for this. The relative non-invasive nature of LTCBDE compared to transgastric ERC may allow surgeons a more liberal approach to smaller stones. It is therefore relatively easy to ensure that the patient is free from CBD stones, rather than trusting the spontaneous passage of incidental small stones. Another explanation may be that the ERC group had more patients with symptomatic stones, i.e. with a preoperative suspicion by icterus or raised bilirubin levels, which may have been larger in size as a consequence. As larger stones are more difficult to manage with the LTCBDE technique, stone size may have had an influence on the surgeon's choice of intervention. The shorter operating time and shorter postoperative stay for LTCBDE could possibly be explained by the fewer number of acute cases in this group.

Since an intraoperative transgastric ERC simply required the introduction of a laparoscopy-assisted transgastric access route to enable an otherwise standard ERC technique, this approach may be preferable if the ERC procedure is already readily available.[138-143] The other option, the LTCBDE technique, is a proven technique that has been in use for over 20 years.[144-145] It is minimally invasive, resource-effective, non-specific to the Roux-en-Y anatomy, and has a modest learning curve. [159] As the technique works for any patient, it can enable surgeons to perform a single-stage procedure on their RYGB patients as well as any other patients, which is preferable when a new technique needs to be implemented.

Conclusions

The papers in this thesis highlight different important aspects of late surgical complications of Roux-en-Y gastric bypass, such as acute and chronic abdominal pain, internal herniations, intussusceptions, and common bile duct stones. Our findings confirm the high number of patients suffering from unspecific abdominal pain as well as chronic abdominal pain. Further, they highlight that the most common complication, internal herniation, can occur and reoccur at any time after the RYGB surgery.

Study-specific conclusions:

I. In **Paper I** we showed that a significant subset of Roux-en-Y gastric bypass operated patients admitted for acute abdominal pain had no confirmed diagnosis at discharge (48%), despite extensive diagnostic work-up including computed tomography (75%) and diagnostic laparoscopy (22%). In contrast, nearly half (49%) of the admitted patients underwent acute surgery. Of these, two quarters (66/128) had surgery for a RYGB complication, a quarter (32/128) had another surgical diagnosis, and the final quarter (30/128) had unremarkable diagnostic laparoscopies to rule out a RYGB complication. The most common surgical diagnosis was internal herniation, accounting for a third of all surgeries (42/128). Only 24% (69/282) of patients were discharged with a diagnosis unrelated to the RYGB.

   In a government-funded healthcare system, with limited resources, it would be desirable to reduce the number of admissions, any unnecessary and potentially harmful repeated CT scans, and explorative laparoscopies without putting the patients at risk. Better tools for the evaluation of acute abdominal pain and a greater understanding of the cause of abdominal pain in a large subset of these patients requires further study.

II. In **Paper II**, a long-term follow-up of surgery for internal herniation, we reported that 12% of patients had a recurrence at the untreated mesenteric gap during a six-year follow-up. However, no recurrences occurred at the repaired mesenteric gaps. This emphasizes the importance of carefully investigating weaknesses or gaps at both mesenteric gaps at the surgery for internal

herniation. Furthermore, the six patients operated on by bariatric surgeons did not suffer any recurrences.

III. In **Paper III** we showed that patients with internal herniation have few biochemical measurable changes in the blood. The biomarkers citrulline, I-FABP, and D-dimer, unfortunately, do not show promise as diagnostic tools and so far no useful diagnostic biomarker has been discovered. The study also highlights the need for better diagnostic tools in Roux-en-Y gastric bypass operated patients with acute abdominal pain and shows that simple assessment of pain level or duration, with the knowledge we have today, cannot be used as a diagnostic tool for the clinician. Further studies are needed to help gauge the clinician's suspicion of internal herniation and possible vascular compromise. Since laboratory tests and computed tomography scans cannot reliably rule out an internal herniation, surgeons must liberally perform explorative laparoscopies as the gold standard to rule out an internal herniation in Roux-en-Y gastric bypass patients with acute abdominal pain.

IV. In **Paper IV** we showed that intussusception length on an acute abdominal computed tomography correlated to the risk for bowel obstruction. We proposed that an intussusception length of more than 100mm be used as an easy and useful radiological sign in acute abdominal CTs indicating small bowel obstruction in Roux-en-Y gastric bypass patients with acute abdominal pain. We encourage surgeons to collaborate closely with radiologists to differentiate patients in need of emergency surgery.

V. In **Paper V**, we showed that both laparoscopic transcystic common bile duct exploration and intraoperative ERC procedures were used for extraction of common bile duct stones during cholecystectomy in Roux-en-Y gastric bypass patients with good outcome and low adverse event rates. LTCBDE was significantly faster and more often used for smaller common bile duct stones. ERC was more often used in the acute setting and in conjunction with larger stones.

Methodological considerations

The first four studies, **Paper I-IV**, were all single-center studies that could have benefitted from widening the perspective and being multi-center studies instead. The studies could also benefit from being repeated and confirmed elsewhere, for the results to be more generalizable. Multi-center studies, on the other hand, offer a larger sample size of the population in a shorter time and the results become more generalizable. The drawback of a multi-center study is the added administration, cost, and logistics, as well as difficulties in protocol adherence that may occur because of differences in routines and settings between hospitals.

Papers I, II, and IV were retrospective cohort studies that have the known disadvantage of missing data. Some variables could not be evaluated because of the amount of missing data. Analysis of the missing data can also be difficult, as there may be bias in which data is missing. **Papers I** had the benefit of prospective inclusion, which reduced the risk of missing patients in the cohort.

Follow-up data in our cohorts, in particular in **Paper I and II**, had very few patients lost to follow-up, because of the digital access to all emergency departments and acute surgical wards for the region of Scania (Skåne).

Paper III was a prospective study, where the included variables could be controlled. The patient inclusion process in such a study requires a lot of time and effort and inevitably not every patient is enrolled, which may incur a bias in the study.

The usage of validated national registries with excellent coverage over a 10-year period was a major strength of **Paper V**.[159-162] The study cohort of RYGB patients with CBD stones allowed for the largest intervention comparison of its kind. Since both investigated techniques, LTCBDE and transgastric ERC, have been used in Sweden for many years, the study design using GallRiks enabled comparison of the procedures in a relatively large cohort, given the rare condition. Study limitations included inherent limitations of specific variables from the registry data, that e.g. did not explain the exact means by which the intra-operative ERC was performed. In addition, registration was done postoperatively, and a failed or aborted procedure may not have been reported, as only the final procedure was registered. There may also be bias in the chosen procedure. Either a bias of procedure choice if more than one procedure was available, or a bias

incurred by the fact that most hospitals may not have had access to more than one procedure. Similar to retrospective studies some data can be missing and an analysis of the missing data is difficult but can be a cause of bias. Nevertheless, the strength of the study size outweighs the limitations.

A strength of this thesis project was that all research questions were drawn from clinical practice with the results having direct application to the patients that we treat on a daily basis.

Future perspectives

Late surgical complications are an important reason for Roux-en-Y gastric bypass operations slowly losing in popularity in favor of other bariatric procedures. A lot of effort has been put in place to reduce the incidence of internal herniations, particularly the routine closure of the mesenteric gaps. These efforts need to continue and it is important that surgeons around the country are aware of the importance of closing open mesenteric gaps during any abdominal surgery, as there are still patients with open defects at risk of internal herniation.

The internal herniations do not, however, explain the large proportion of patients suffering from chronic abdominal pain. There are several studies that report a high prevalence (10-33%) of chronic abdominal pain in these patients, however, little effort has been made in trying to find an explanation for it. What is the cause of the abdominal pain, when no pathology is found in laboratory tests, imaging, or diagnostic laparoscopy? Some patients with chronic pain seem to improve following the closure of the mesenteric gaps, indicating that intermittent herniations may be the cause. Others improve after complete revisions of their jejunojejunostomy, indicating that intermittent intussusceptions may be the cause. Yet others may improve following the complete reversal of their gastric bypass, which is often used as a last resort at the patient's desperate request. Surgeons cannot guarantee symptom relief, although significant weight rebound is certain. However, neither surgery is performed with any scientific certainty of symptom relief, as only some patients seem to benefit. Unfortunately, there still remain patients with chronic abdominal pain for whom no specific treatment is available, and what is worse is that no explanation can be given for the cause of the pain. Joint efforts in investigating the abdominal pain in these patients are necessary.

The pain experienced in these patients can be referred to as functional abdominal pain and can be likened to visceral hyperalgesia which is commonly associated with functional abdominal pain in children. This condition is only sometimes postoperative in children and is often associated with other psychiatric disorders, not unlike bariatric surgery patients. Although, it is important to remember that an underlying psychiatric condition is by no means obligatory to suffer from functional abdominal pain. The

prognosis in children is much better though as most outgrow their disease and perhaps a partnership with interested pediatricians can be fruitful in developing strategies to handle post-RYGB patients with chronic abdominal pain.

A key issue, however, is that of the ownership of these patients. Most bariatric procedures are performed by private clinics with 30-day responsibility for early complications. Late surgical complications and chronic pain are often left to acute care surgeons in our government-financed healthcare system. When no surgically treatable condition is found and a diagnosis of functional chronic abdominal pain is made the patients are referred back to their primary care physician with limited knowledge of how to treat the problem. Patients may even have been started on opioids during acute hospital admission and the primary care physician is left with having to detox the patient, a difficult task for anyone dealing with chronic pain patients. Patients with chronic pain without a malignant cause are unfortunately under prioritized in our healthcare system and these patients have few options other than their primary care physician.

In a broader sense, it is important to let our politicians know that advanced chronic pain management clinics need to be set up in order to manage patients with non-malignant chronic pain conditions. It is only by increasing the number of patients that studies can be performed to improve the management and outcome of chronic pain conditions.

Intussusception is another interesting condition that occurs with an increased frequency in RYGB patients and only sometimes leads to bowel obstruction. It is unclear if the majority of intussusceptions are symptomatic or not. Perhaps they are merely a visual indication of the disrupted peristalsis by the Roux-en-Y reconstruction? Further studies into the clinical implication of these intussusceptions are necessary. A multicenter study would be necessary to evaluate outcomes of revisional surgery for repeated intussusceptions, with a main focus on quality of life and pain relief.

Treatment of common bile duct stones in gastric bypass patients has forced the invention of a new technique, transgastric ERC, and perhaps also accelerated the introduction of transcystic common bile duct exploration. Either method showed good results in clearing the common bile duct in our study and perhaps they will soon eliminate the need for open or laparoscopic choledochotomy, with the risk of morbidity that goes with it. A follow-up study in about five years would be able to show the development and distribution of the techniques across the country and evaluate outcome over time. Hopefully the techniques will be used for a greater proportion of patients compared to the current 50%. A larger material would also be able to better distinguish small differences in outcome between the techniques.

Populärvetenskaplig sammanfattning på svenska

Denna kliniska doktorsavhandling utgår ifrån fem studier, som var och en undersöker sena kirurgiska komplikationer till vår genom tiderna vanligaste överviktsoperation, gastric bypass operation. Avhandlingen är uppbyggd och skriven ur ett akutkirurgiskt perspektiv, men ramberättelsen innehåller en översikt om överviktskirurgi som alla med intresse av överviktskirurgi kan ha glädje av.

Första arbetet analyserade diagnoser och utfall för 282 tidigare Roux-en-Y gastric bypass opererade patienter, som vårdats för akut buksmärta vid Skånes Universitetssjukhus i Malmö mellan april 2012 och juni 2015. Studien visade att närmre hälften av patienterna skrevs ut utan att någon förklaring till deras akuta buksmärta hade diagnosticerats, trots utförlig utredning med skiktröntgen (75%) och titthålskirurgi (22%). Dessa patienter hade dessutom fler återinläggningar under uppföljningstiden. Samtidigt genomgick hälften av patienterna akuta eller subakuta operationer.

Operationer för komplikationer till gastric bypass operationen utgjorde hälften av dessa ingrepp, medan ytterligare en fjärdedel genomgick diagnostiska titthålsoperationer där inget avvikande påträffats. Dessa titthålsoperationer utfördes alltjämt för att man befarade den vanligaste komplikationen efter gastric bypass, sk. slitsherniering eller inklämt inre bråck. Slitsherniering utgjorde två tredjedelar av alla komplikationer och innebär att tunntarmen fastnar och stryps i en av de två inre springor (slitsar) som uppstår när tarmkexen delas och tarmen kopplas om vid gastric bypass operationen. Vi visade att slitshernieringarna kunde inträffa när som helst efter gastric bypass operationen och trots att de inre springorna i vissa fall redan var förslutna. Endast en fjärdedel av operationerna var för andra vanliga kirurgiska diagnoser däribland gallblåseoperation, som var vanligast. Gallstenssjukdom är vanligare bland överviktiga och risken ökar ytterligare vid hastig viktnedgång såsom efter överviktskirurgi.

Studie II. var en sex års-uppföljning av 51 patienter som opererats för slitsherniering. Vi fann att 12% av patienterna fick återfall som krävde nya operationer. Inga återfall uppkom i slitsen som slöts vid första tillfället utan samtliga uppkom i den andra av de två inre slitsarna. De flesta patienterna hade opererats av allmänkirurger utan särskild

vana vid överviktsoperationer. De sex patienterna som opererats av kirurger med erfarenhet av överviktskirurgi fick inga återfall. Då över hälften av operationerna utförts på jourtid är det ibland svårt att se till att ha sådan kompetens på plats.

Diagnosen slitsherniering är erkänt svår att ställa och orsak till många titthåls-operationer som görs i syfte att utesluta tillståndet. I studie III. utvärderade vi blodprover för tarmskademarkörerna citrulline, Intestinal-Fattyacid binding protein och D-dimer i syfte att bedöma om dessa tarmskademarkörer kan urskilja patienter med diagnosen slitsherniering. I samband med inläggning på sjukhus för akut buksmärta tillfrågades patienter för deltagande i studien varpå akuta blodprover togs vid inläggningen och vid en eventuell akut operation. Patienterna ombads också att fylla i ett smärtskattningsformulär och svara på frågor om sin sjukhistoria. Vid utvärdering av blodproverna påvisades dock inga skillnader eller samband för de tre undersökta markörerna eller för tre vanliga akutprover (CRP, vita blodkroppar och laktat) för patienter som drabbats av slitsherniering. Smärtskattningsformuläret påvisade inte heller några skillnader mellan de olika diagnoserna. Således kan varken tarmskademarkörer eller smärtnivå användas i syfte att ställa diagnosen slitsherniering.

Studie IV var ett samarbete med vår röntgenavdelning. Vi studerade tillsammans de tunntarmsinvaginationer som ses på skiktröntgen och som uppstår betydligt oftare efter en gastric bypass operation. En invagination uppkommer av att tarmens peristaltik fastnar i en tarmförändring som gör att den matas in i sig självt, dvs. invagineras. Varför det sker hos gastric bypass opererade är oklar, men ett par olika teorier har föreslagits. Flertalet invaginationer tycks släpper spontant utan att ge några följder. Andra gånger kan tarmen dock fastna och orsakar då ett allvarligt tarmvred som kräver snar operation innan tarmen tar skada. Genom att utvärdera särskilda tecken på röntgenbilderna och jämföra vilka patienter som fick tarmvred var syftet att förbättra bedömningen av dessa patienter så att kirurger ska ha lättare att urskilja patienter med allvarlig invagination. Två röntgenläkare eftergranskade 35 patienters skiktröntgenbilder utifrån ett protokoll som sedan jämfördes mot en journalgranskning av utfallet av vården och operationerna. Studien gav ny kunskap som visade att invaginationer som var längre än 10 cm hade stor risk för att orsaka tarmvred, medan kortare invaginationer oftast löste sig spontant.

Överviktiga samt de som hastigt går ner i vikt, så som efter en överviktsoperation, har en ökad risk att utveckla gallstenssjukdom. Gallstenar i de djupa gallvägarna utgör ett särskilt bekymmer hos gastric bypass opererade, eftersom operationen innebär att magsäcken och tolvfingertarmen är förbikopplade, vilket omöjliggör den vanligaste kameraundersökningen av gallgångarna, så kallad endoskopisk retrograd kolangiopankreatikografi, ERCP. Istället måste andra tekniker användas, så som transgastrisk ERC eller laparoskopisk transcystisk stenextraktion. Vid 7-18% av planerade gallblåseoperationer och ännu oftare vid akuta operationer påträffas stenar

också i de djupa gallvägarna. Transgastrisk ERC utförs som en vanlig ERCP, men genom att man vid gallblåseoperationen öppnar magsäcken och för in endoskopet genom en port för att på så sätt få tillgång till tolvfingertarmen och gallvägarna. Laparoskopisk transcystisk stenextraktion utförs genom att en tunn (2.8 mm) kamera som förs in i gallgången som förbinder gallblåsan med gallvägarna (ductus cysticus) i samband med att denna struktur delas vid gallblåseoperationen. Man kan på så sätt nå och behandla stenarna i gallvägarna. Båda metoderna har fördelen att patienten blir färdigbehandlad vid samma operationstillfälle och har visat sig ha goda resultat var för sig, men har inte tidigare jämförts mot varandra. Vi utförde en databasstudie, genom att för en 10-års period (2011-2020) söka efter gastric bypass opererade patienter som genomgått behandling av stenar i de djupa gallvägarna i de nationella kvalitetsregistren för gallstenssjukdom (GallRiks) och överviktskirurgi (SOReg). Studien visade att bägge teknikerna kunde utföras framgångsrikt, säkert, och med få komplikationer.

Nyhetsvärde

Avhandlingsarbetet har bidragit till vår kunskap om flera sena kirurgiska komplikationer till gastric bypass operationen. Våra resultat bekräftade att den absolut vanligaste komplikationen är inre bråck, s.k. slitsherniering, där tarmen fastnar i ett av två springor i tarmkexet. Slitsherniering kan uppträda när som helst efter operationen och kräver noggrann operation av bägge slitsarna helst utförd av kirurg med vana av överviktskirurgi eftersom återfallsrisken är stor. Skiktröntgen är den bästa metoden för att ställa diagnosen, men bedömningen kan vara svår. Smärtanamnes och blodprover ger sällan hjälp, utan om misstanken uppstår bör kirurger frikostigt utföra titthålsoperationer för att utesluta slitsherniering och undersöka om slitsarna är förslutna. Slitsförslutning minskar återfallsrisken men utesluter den inte helt.

Vidare visade vår studie av tunntarmsinvaginationer hos gastric bypass patienter att de med långa invaginationer, längre än 10 cm, har en betydande risk för tarmvred, medan kortare invaginationer ofta går över av sig självt. Detta är ny värdefull information för röntgenläkare och för kirurger som ska ta kliniska beslut.

Slutligen visade våra studier att de två vanligast förekommande operationsteknikerna för behandling av gallsten i de djupa gallvägarna hos gastric bypass opererade, transgastrisk ERC och transcystisk stenextraktion, bägge är framgångsrika med ett lågt antal komplikationer.

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to live a pleasant life,
either in someone's heart
or in someone's prayer."
– Imam Ali (AS)

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References

1. V Henrikson. Kan tunntarmsresektion försvaras som terapi mot fettsot - Nordisk Medicin, 1952; 30:744
2. Faria GR. A brief history of bariatric surgery. Porto Biomed J. 2017;2(3):90-92. doi:10.1016/j.pbj.2017.01.008
3. Kremen, Arnold J. M.D.; Linner, John H. M.D; Nelson, Charles H. M.D.. An experimental evaluation of the nutritional importance of proximal and distal small intestine. Annals of Surgery: September 1954; 140 (3): p 439-448
4. Celio AC, Pories WJ. A History of Bariatric Surgery: The Maturation of a Medical Discipline. Surg Clin North Am. 2016;96(4):655-667. doi:10.1016/j.suc.2016.03.001
5. Edward E. Mason, Chikashi Ito, Gastric Bypass in Obesity, Surgical Clinics of North America, 1967; 47 (6): p 1345-1351 doi.org/10.1016/S0039-6109(16)38384-0.
6. MacLean, L.D. Progress in the Treatment of Obesity. Obes Surg 1996; 6, 398–405. doi.org/10.1381/096089296765556458
7. Ito C, Mason EE, Besten LD. Experimental studies on gastric bypass versus standard ulcer operations. Tohoku J Exp Med. 1969;97(3):269-277. doi:10.1620/tjem.97.269
8. Wittgrove, A.C., Clark, G.W. & Tremblay, L.J. Laparoscopic Gastric Bypass, Roux-en-Y: Preliminary Report of Five Cases. Obes Surg 4, 1994; p 353–357 doi.org/10.1381/096089294765558331
9. Lönroth H, Dalenbäck J, Haglind E, Lundell L. Laparoscopic gastric bypass. Another option in bariatric surgery. Surg Endosc. 1996 Jun;10(6):636-8.
10. Sundbom M, Karlson BM. Low mortality in bariatric surgery 1995 through 2005 in Sweden, in spite of a shift to more complex procedures. Obes Surg. 2009;19(12):1697-1701. doi:10.1007/s11695-008-9684-7
11. Leffler E, Gustavsson S, Karlson BM. Time trends in obesity surgery 1987 through 1996 in Sweden--a population-based study. Obes Surg. 2000;10(6):543-548. doi:10.1381/096089200321593760
12. Marsk R, Freedman J, Tynelius P, Rasmussen F, Näslund E. Antiobesity surgery in Sweden from 1980 to 2005: a population-based study with a focus on mortality. Ann Surg. 2008;248(5):777-781. doi:10.1097/SLA.0b013e318189b0cf

13. Adams TD, Gress RE, Smith SC, et al. Long-term mortality after gastric bypass surgery. N Engl J Med. 2007;357(8):753-761. doi:10.1056/NEJMoa066603
14. H. Buchwald, D.M. Oien. Metabolic/bariatric surgery worldwide 2011. Obesity Surg, 23 (2013), pp. 427-436, doi.org/10.1007/s11695-012-0864-0
15. Printen KJ, Scott D, Mason EE. Stomal ulcers after gastric bypass. Arch Surg. 1980;115(4):525-527. doi:10.1001/archsurg.1980.01380040147026
16. Siilin H, Wanders A, Gustavsson S, Sundbom M. The proximal gastric pouch invariably contains acid-producing parietal cells in Roux-en-Y gastric bypass. Obes Surg. 2005;15(6):771-777. doi:10.1381/0960892054222849
17. Wilkinson LH, Peloso OA. Gastric (reservoir) reduction for morbid obesity. Arch Surg. 1981;116(5):602-605. doi:10.1001/archsurg.1981.01380170082014
18. Gaidry AD, Tremblay L, Nakayama D, Ignacio RC Jr. The History of Surgical Staplers: A Combination of Hungarian, Russian, and American Innovation. Am Surg. 2019;85(6):563-566.
19. Robicsek F. The birth of the surgical stapler. Surg Gynecol Obstet. 1980;150(4):579-583.
20. Mason EE. Vertical banded gastroplasty for obesity. Arch Surg. 1982;117(5):701-706. doi:10.1001/archsurg.1982.01380290147026
21. Bö O, Modalsli O: Gastric banding, a surgical method of treating morbid obesity: preliminary report. Int J Obes 1983; 7: 493-9
22. Solhaug JH: Gastric banding: a new method in the treatment of morbid obesity. Current Surgery 1983; 88: 423-8
23. Forsell P, Hallberg D, Hellers G. A Gastric Band with Adjustable Inner Diameter for Obesity Surgery: Preliminary Studies. Obes Surg. 1993;3(3):303-306. doi:10.1381/096089293765559368
24. Kuzmak LI. A Review of Seven Years' Experience with Silicone Gastric Banding. Obes Surg. 1991;1(4):403-408. doi:10.1381/096089291765560809
25. P. Forsell, G. Hellers. The Swedish Adjustable Gastric Banding (SAGB) for morbid obesity: 9 year experience and a 4-year follow-up of patients operated with a new adjustable band. Obesity Surg, 7 (1997), pp. 345-351, doi:10.1381/096089297765555601
26. Cadière GB, Bruyns J, Himpens J, Favretti F. Laparoscopic gastroplasty for morbid obesity. Br J Surg. 1994;81(10):1524. doi:10.1002/bjs.1800811042
27. Belachew M, Legrand M, Vincenti V V, et al. Laparoscopic Placement of Adjustable Silicone Gastric Band in the Treatment of Morbid Obesity: How to Do It. Obes Surg. 1995;5(1):66-70. doi:10.1381/096089295765558196
28. P. Marceau, S. Biron, R. Bourque, M. Potvin, F. Hould, S. Simard. Biliopancreatic diversion with a new type of gastrectomy. Obesity Surg, 3 (1993), pp. 29-35, doi:10.1381/096089293765559728

29. D.S. Hess, D.W. Hess. Biliopancreatic diversion with a duodenal switch. Obesity Surg, 8 (1998), pp. 267-282, doi:10.1381/096089298765554476
30. Chu C, Gagner M, Quinn T, Voellinger DC, Feng JJ, Inabnet WB, Herron D, Pomp A: Two-stage laparoscopic BPD/DS. An Alternative Approach To Super-Super Morbid Obesity. Surgical Endoscopy 2002; S187
31. Sanchez-Pernaute A, Rubio Herrera MA, Perez- Aguirre E, Garcia Perez JC, Cabrerizo L, Diez Valladares L. Proximal duodenal-ileal end-to-side bypass with sleeve gastrectomy: proposed technique. Obes Surg. 2007;17(12):1614–8. doi: 10.1007/s11695-007-9287-8
32. Sánchez-Pernaute A, Rubio MÁ, Pérez N, Marcuello C, Torres A, Pérez- Aguirre E, Single-anastomosis duodeno-ileal bypass as a revisional or second-step operation after sleeve gastrectomy, Surgery for Obesity and Related Diseases (2020), doi:10.1016/ j.soard.2020.05.022.
33. Garcia-Caballero, M. and M. Carbajo, One anastomosis gastric bypass: a simple, safe and efficient surgical procedure for treating morbid obesity. Nutr Hosp, 2004. 19(6): p. 372-5.
34. Magouliotis DE, Tasiopoulou VS, Tzovaras G. One Anastomosis Gastric Bypass Versus Roux-en-Y Gastric Bypass for Morbid Obesity: an Updated Meta-Analysis. Obes Surg. 2019;29(9):2721-2730. doi:10.1007/s11695-019-04005-0
35. Stavropoulos SN, Modayil R, Friedel D. Current applications of endoscopic suturing. World J Gastrointest Endosc. 2015;7(8):777-789. doi:10.4253/wjge.v7.i8.777
36. Yoon JY, Arau RT; Study Group for Endoscopic Bariatric and Metabolic Therapies of the Korean Society of Gastrointestinal Endoscopy. The Efficacy and Safety of Endoscopic Sleeve Gastroplasty as an Alternative to Laparoscopic Sleeve Gastrectomy. Clin Endosc. 2021;54(1):17-24. doi:10.5946/ce.2021.019
37. Brunaldi VO, Jirapinyo P, de Moura DTH, et al. Endoscopic Treatment of Weight Regain Following Roux-en-Y Gastric Bypass: a Systematic Review and Meta-analysis. Obes Surg. 2018;28(1):266-276. doi:10.1007/s11695-017-2986-x
38. Jirapinyo P, de Moura DTH, Thompson CC. Sleeve in sleeve: endoscopic revision for weight regain after sleeve gastrectomy. VideoGIE. 2019;4(10):454-457. Published 2019 Aug 13. doi:10.1016/j.vgie.2019.07.003
39. Pories WJ, Swanson MS, MacDonald KG, et al. Who would have thought it? An operation proves to be the most effective therapy for adult-onset diabetes mellitus. Ann Surg. 1995;222(3):339-352. doi:10.1097/00000658-199509000-00011
40. Henry Buchwald, Richard L Varco. Metabolic Surgery. 235 × 155 mm. Pp. 317, with 57 illustrations. 1978. New York: Grune & Stratton.
41. Sjöström L. SOS--en interventionsstudie av fetma [Swedish Obese Subjects--an intervention study on obesity]. Lakartidningen. 1988;85(8):636-639.

42. Sjöström L, Narbro K, Sjöström CD, et al.. Effects of bariatric surgery on mortality in Swedish obese subjects. N Engl J Med 2007;357:741–52. doi:10.1056/NEJMoa066254
43. Sjöström L. Bariatric surgery and reduction in morbidity and mortality: experiences from the SOS study. Int J Obes (Lond). 2008;32 Suppl 7:S93-S97. doi:10.1038/ijo.2008.244
44. Sjöström L, Peltonen M, Jacobson P, et al. Bariatric surgery and long-term cardiovascular events. JAMA. 2012;307(1):56-65. doi:10.1001/jama.2011.1914
45. Sjöström L. Review of the key results from the Swedish Obese Subjects (SOS) trial - a prospective controlled intervention study of bariatric surgery. J Intern Med. 2013;273(3):219-234. doi:10.1111/joim.12012
46. World Health Organization. Obesity: preventing and managing the global epidemic, Report of a WHO Consultation, 2000 Geneva, Switzerland (WHO technical report series 894)
47. National Heart, Lung, and Blood Institute – NIH. (1998). Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: the evidence report. 98(4083) Accessed Sept 2022 from http://www.nhlbi.nih.gov/guidelines/obesity/ob_gdlns.pdf
48. American Medical Association (2013) Recognition of Obesity as a Disease. H-440.842. https://policysearch.ama-assn.org/policyfinder/detail/H-440.842?uri=%2FAMADoc%2FHOD.xml-0-3858.xml
49. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128·9 million children, adolescents, and adults. Lancet. 2017;390(10113):2627-2642. doi:10.1016/S0140-6736(17)32129-3
50. World Health Organization. Noncommunicable diseases country profiles 2018, World Health Organization, Geneva (2018)
51. National Center for Health Statistics, National Health and Nutrition Examination Survey, 2017–March 2020 prepandemic data files https://www.cdc.gov/nchs/data/nhsr/nhsr158-508.pdf
52. Folkhälsomyndigheten. Övervikt och fetma [Internet]. Stockholm: Folkhälsomyndigheten; 2022. https://www.folkhalsomyndigheten.se/fu-overvikt-och-fetma. Published March 23rd 2022, Accessed October 2nd 2022.
53. Hedenbro JL, Näslund E, Boman L, et al. Formation of the Scandinavian Obesity Surgery Registry, SOReg. Obes Surg. 2015;25(10):1893-1900. doi:10.1007/s11695-015-1619-5

54. Sundbom M, Näslund I, Näslund E, Ottosson J. High acquisition rate and internal validity in the Scandinavian Obesity Surgery Registry. Surg Obes Relat Dis. 2021;17(3):606-614. doi:10.1016/j.soard.2020.10.017
55. Tao W, Holmberg D, Näslund E, Näslund I, Mattsson F, Lagergren J, et al. Validation of obesity surgery data in the swedish national patient registry and scandinavian obesity registry (SOReg). Obes Surg. (2015) 26:1750–6. doi:10.1007/s11695-015-1994-y
56. Enochsson L, Thulin A, Osterberg J, Sandblom G, Persson G. The Swedish Registry of Gallstone Surgery and Endoscopic Retrograde Cholangiopancreatography (GallRiks): A nationwide registry for quality assurance of gallstone surgery. JAMA Surg. 2013;148(5):471-478. doi:10.1001/jamasurg.2013.1221
57. Enochsson L, Swahn F, Arnelo U, Nilsson M, Löhr M, Persson G. Nationwide, population-based data from 11,074 ERCP procedures from the Swedish Registry for Gallstone Surgery and ERCP. Gastrointest Endosc. 2010;72(6):1175-1184.e11843. doi:10.1016/j.gie.2010.07.047
58. The Swedish National Board of Health and Welfare - Täckningsgrader för Nationella kvalitetsregister 2020. https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/artikelkatalog/statistik/2020-12-7049.pdf Published December 4th 2020, Accessed September 9th 2022.
59. Scandinavian Obesity Surgery Registry – Annual report 2021 del 1, p.4-8 https://www.ucr.uu.se/soreg/component/edocman/soreg-annual-report-2021-part-1/download?Itemid= Published August 9, 2022. Accessed October 3rd, 2022.
60. Estimate of Bariatric Surgery Numbers, 2011-2020. (2022, June 27). American Society for Metabolic and Bariatric Surgery. https://asmbs.org/resources/estimate-of-bariatric-surgery-numbers
61. Socialstyrelsen. Nationella riktlinjer för vård vid obesitas. Stöd för styrning och ledning 2022. https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/artikelkatalog/nationella-riktlinjer/2022-4-7822.pdf
62. Rubino F, Nathan DM, Eckel RH, et al. Metabolic Surgery in the Treatment Algorithm for Type 2 Diabetes: A Joint Statement by International Diabetes Organizations. Diabetes Care. 2016;39(6):861-877. doi:10.2337/dc16-0236
63. Jacobsen HJ, Nergard BJ, Leifsson BG, et al. Management of suspected anastomotic leak after bariatric laparoscopic Roux-en-y gastric bypass. *Br J Surg*. 2014;101(4):417-423. doi:10.1002/bjs.9388
64. Quartararo G, Facchiano E, Scaringi S, Liscia G, Lucchese M. Upper gastrointestinal series after Roux-en-Y gastric bypass for morbid obesity: effectiveness in leakage detection. a systematic review of the literature. Obes Surg. 2014;24(7):1096-1101. doi:10.1007/s11695-014-1263-5

65. Podnos YD, Jimenez JC, Wilson SE, Stevens CM, Nguyen NT. Complications after laparoscopic gastric bypass: a review of 3464 cases. Arch Surg. 2003;138(9):957-961. doi:10.1001/archsurg.138.9.957
66. Keith JN . Endoscopic management of common bariatric surgical complications. Gastrointest Endosc Clin N Am 2011;**21**:275-85. doi:10.1016/j.giec.2011.02.007
67. Freedman J, Jonas E, Näslund E, Nilsson H, Marsk R, Stockeld D. Treatment of leaking gastrojejunostomy after gastric bypass surgery with special emphasis on stenting. Surg Obes Relat Dis. 2013;9(4):554-558. doi:10.1016/j.soard.2012.03.002
68. Rondelli F, Bugiantella W, Vedovati MC, et al. Laparoscopic gastric bypass versus laparoscopic sleeve gastrectomy: A retrospective multicenter comparison between early and long-term post-operative outcomes. Int J Surg. 2017;37:36-41. doi:10.1016/j.ijsu.2016.11.106
69. Pereira A, Santos RF, Costa-Pinho A, et al. Early Postoperative Bleeding After Laparoscopic Roux-En-Y Gastric Bypass: a Single Center Analysis. Obes Surg. 2022;32(6):1902-1908. doi:10.1007/s11695-022-05973-6
70. Odovic M, Clerc D, Demartines N, Suter M. Early Bleeding After Laparoscopic Roux-en-Y Gastric Bypass: Incidence, Risk Factors, and Management - a 21-Year Experience. Obes Surg. 2022;32(10):3232-3238. doi:10.1007/s11695-022-06173-y
71. Zafar, S.N., Miller, K., Felton, J. et al. Postoperative bleeding after laparoscopic Roux en Y gastric bypass: predictors and consequences. Surg Endosc **33**, 272–280 (2019). https://doi.org/10.1007/s00464-018-6365-z
72. Stenberg E, Szabo E, Ågren G, Ottosson J, Marsk R, Lönroth H, Boman L, Magnuson A, Thorell A, Näslund I. Closure of mesenteric defects in laparoscopic gastric bypass: a multicentre, randomised, parallel, open-label trial. Lancet. 2016 Apr 2;387(10026):1397-1404. doi:10.1016/S0140-6736(15)01126-5
73. Poelemeijer YQM, Liem RSL, Våge V, et al. Perioperative Outcomes of Primary Bariatric Surgery in North-Western Europe: a Pooled Multinational Registry Analysis. Obes Surg. 2018;28(12):3916-3922. doi:10.1007/s11695-018-3408-4
74. Bradley JF 3rd, Ross SW, Christmas AB, Fischer PE, Sachdev G, Heniford BT,Sing RF. Complications of bariatric surgery: the acute care surgeon's experience. Am J Surg. 2015 Sep;210(3):456-61. doi:10.1016/j.amjsurg.2015.03.004
75. Wernick B, Jansen M, Noria S, Stawicki SP, El Chaar M. Essential bariatric emergencies for the acute care surgeon. Eur J Trauma Emerg Surg. 2016;42(5):571-584. doi:10.1007/s00068-015-0621-x
76. Schulman AR, Thompson CC. Abdominal Pain in the Roux-en-Y Gastric Bypass Patient. Am J Gastroenterol. 2018;113(2):161-166. doi:10.1038/ajg.2017.361

77. De Simone B, Chouillard E, Ramos AC, et al. Operative management of acute abdomen after bariatric surgery in the emergency setting: the OBA guidelines. World J Emerg Surg. 2022;17(1):51. Published 2022 Sep 27. doi:10.1186/s13017-022-00452-w
78. Petersen W. Ueber darmveschlingung nach der gastro-enterostomie. Arch Klin Chir. 1900;62:94–114.
79. Leifsson BG, Gislason HG. Laparoscopic Roux-en-Y gastric bypass with 2-metre long biliopancreatic limb for morbid obesity: technique and experience with the first 150 patients. Obes Surg. 2005;15(1):35-42. doi:10.1381/0960892052993396
80. Brammerloo YGA, Vannijvel M, Devriendt S, et al. Internal Hernia After Laparoscopic Gastric Bypass Without Preventive Closure of Mesenteric Defects: a Single Institution's Experience. J Gastrointest Surg. 2021;25(3):623-634. doi:10.1007/s11605-020-04761-w
81. Aghajani E, Nergaard BJ, Leifson BG, Hedenbro J, Gislason H. The mesenteric defects in laparoscopic Roux-en-Y gastric bypass: 5 years follow-up of non-closure versus closure using the stapler technique. Surg Endosc. 2017;31(9):3743-3748. doi:10.1007/s00464-017-5415-2.
82. Al-Mansour MR, Mundy R, Canoy JM, Dulaimy K, Kuhn JN, Romanelli J. Internal Hernia After Laparoscopic Antecolic Roux-en-Y Gastric Bypass. Obes Surg. 2015;25(11):2106-2111. doi:10.1007/s11695-015-1672-0
83. M.Ekelund, E Näslund. Expertgruppsrekommendationer för slitsar vid laparoskopisk Gastric bypass. SFOK, SOReg. https://www.ucr.uu.se/soreg/dokument/dokument/expertgruppsrekommendationer-foer-slitsar-vid-lap-gastric-by-pass/viewdocument/86
84. Brolin RE, Kella VN. Impact of complete mesenteric closure on small bowel obstruction and internal mesenteric hernia after laparoscopic Roux-en-Y gastric bypass. Surg Obes Relat Dis. 2013;9(6):850-854. doi:10.1016/j.soard.2012.11.007
85. Chowbey P, Baijal M, Kantharia NS, Khullar R, Sharma A, Soni V. Mesenteric Defect Closure Decreases the Incidence of Internal Hernias Following Laparoscopic Roux-En-Y Gastric Bypass: a Retrospective Cohort Study. Obes Surg. 2016;26(9):2029-2034. doi:10.1007/s11695-016-2049-8
86. Kristensen SD, Gormsen J, Naver L, Helgstrand F, Floyd AK. Randomized clinical trial on closure versus non-closure of mesenteric defects during laparoscopic gastric bypass surgery. Br J Surg. 2021;108(2):145-151. doi:10.1093/bjs/znaa055
87. Geubbels N, Lijftogt N, Fiocco M, van Leersum NJ, Wouters MW, de Brauw LM. Meta-analysis of internal herniation after gastric bypass surgery. Br J Surg. 2015;102(5):451-460. doi:10.1002/bjs.9738

88. Aghajani, E., Jacobsen, H.J., Nergaard, B.J. et al. Internal Hernia After Gastric Bypass: A New and Simplified Technique for Laparoscopic Primary Closure of the Mesenteric Defects. J Gastrointest Surg **16**, 641–645 (2012). doi.org/10.1007/s11605-011-1790-5
89. Stenberg E, Ottosson J, Szabo E, Näslund I. Comparing Techniques for Mesenteric Defects Closure in Laparoscopic Gastric Bypass Surgery-a Register-Based Cohort Study. Obes Surg. 2019;29(4):1229-1235. doi:10.1007/s11695-018-03670-x
90. Nuytens F, D'Hondt M, Van Rooy F, et al. Closure of mesenteric defects is associated with a higher incidence of small bowel obstruction due to adhesions after laparoscopic antecolic Roux-en-y gastric bypass: A retrospective cohort study. Int J Surg. 2019;71:149-155. doi:10.1016/j.ijsu.2019.09.017
91. Stenberg E, Näslund I, Szabo E, Ottosson J. Impact of mesenteric defect closure technique on complications after gastric bypass. Langenbecks Arch Surg. 2018;403(4):481-486. doi:10.1007/s00423-018-1684-z
92. Kristensen SD, Floyd AK, Naver L, Jess P. Does the closure of mesenteric defects during laparoscopic gastric bypass surgery cause complications?. Surg Obes Relat Dis. 2015;11(2):459-464. doi:10.1016/j.soard.2014.10.013
93. Lazaridis II, Köstler T, Kübler L, Zingg U, Delko T. Risk of Reopening of the Mesenteric Defects After Routine Closure in Laparoscopic Roux-en-Y Gastric Bypass: a Single-Centre Experience. Obes Surg. 2022;32(9):2853-2859. doi:10.1007/s11695-022-06179-6
94. Danshøj Kristensen S, Naver L, Jess P, Floyd AK. Reoperation risk following the first operation for internal herniation in patients with laparoscopic Roux-en-Y gastric bypass. Br J Surg. 2016;103(9):1184-1188. doi:10.1002/bjs.10184.
95. Maier J, Herrasti Gallego A, Floyd AK. Compression of the superior mesenteric vein-a sign of acute internal herniation in patients with antecolic laparoscopic Roux-en-Y gastric bypass. Eur Radiol. 2017;27(4):1733-1739. doi:10.1007/s00330-016-4526-9
96. Ederveen JC, van Berckel MMG, Jol S, Nienhuijs SW, Nederend J. Diagnosing internal herniation after laparoscopic Roux-en-Y gastric bypass: usefulness of systematically reviewing CT scans using ten signs. Eur Radiol. 2018;28(9):3583-3590. doi:10.1007/s00330-018-5332-3
97. Dilauro M, McInnes MD, Schieda N, et al. Internal Hernia after Laparoscopic Roux-en-Y Gastric Bypass: Optimal CT Signs for Diagnosis and Clinical Decision Making. *Radiology*. 2017;282(3):752-760. doi:10.1148/radiol.2016160956
98. Iannuccilli JD, Grand D, Murphy BL, Evangelista P, Roye GD, Mayo-Smith W. Sensitivity and specificity of eight CT signs in the preoperative diagnosis of internal mesenteric hernia following Roux-en-Y gastric bypass surgery. Clin Radiol. 2009;64(4):373-380. doi:10.1016/j.crad.2008.10.008

99. Nawas MA, Oor JE, Goense L, et al. The Diagnostic Accuracy of Abdominal Computed Tomography in Diagnosing Internal Herniation Following Roux-en-Y Gastric Bypass Surgery: A Systematic Review and Meta-analysis. *Ann Surg*. 2022;275(5):856-863. doi:10.1097/SLA.0000000000005247

100. Acosta S, Nilsson T. Current status on plasma biomarkers for acute mesenteric ischemia. J Thromb Thrombolysis. 2012;33(4):355-361. doi:10.1007/s11239-011-0660-z

101. Treskes N, Persoon AM, van Zanten ARH. Diagnostic accuracy of novel serological biomarkers to detect acute mesenteric ischemia: a systematic review and meta-analysis. Intern Emerg Med. 2017;12(6):821-836. doi:10.1007/s11739-017-1668-y

102. Memet O, Zhang L, Shen J. Serological biomarkers for acute mesenteric ischemia. Ann Transl Med. 2019;7(16):394. doi:10.21037/atm.2019.07.51

103. Derikx JP, Schellekens DH, Acosta S. Serological markers for human intestinal ischemia: A systematic review. Best Pract Res Clin Gastroenterol. 2017;31(1):69-74. doi:10.1016/j.bpg.2017.01.004

104. Evennett NJ, Petrov MS, Mittal A, Windsor JA. Systematic review and pooled estimates for the diagnostic accuracy of serological markers for intestinal ischemia. World J Surg. 2009;33(7):1374-1383. doi:10.1007/s00268-009-0074-7

105. Treskes N, Persoon AM, van Zanten ARH. Diagnostic accuracy of novel serological biomarkers to detect acute mesenteric ischemia: a systematic review and meta-analysis. Intern Emerg Med. 2017;12(6):821-836. doi:10.1007/s11739-017-1668-y

106. Block T, Nilsson TK, Björck M, Acosta S. Diagnostic accuracy of plasma biomarkers for intestinal ischaemia. Scand J Clin Lab Invest. 2008;68(3):242-248. doi:10.1080/00365510701646264

107. Peoc'h K, Nuzzo A, Guedj K, Paugam C, Corcos O. Diagnosis biomarkers in acute intestinal ischemic injury: so close, yet so far. Clin Chem Lab Med. 2018;56(3):373-385. doi:10.1515/cclm-2017-0291

108. Piton G, Capellier G. Biomarkers of gut barrier failure in the ICU. Curr Opin Crit Care. 2016;22(2):152-160. doi:10.1097/MCC.0000000000000283

109. Ding CM, Wu YH, Liu XF. Diagnostic Accuracy of Intestinal Fatty Acid Binding Protein for Acute Intestinal Ischemia: a Systematic Review and Meta-Analysis. Clin Lab. 2020;66(6):10.7754/Clin.Lab.2019.191139. doi:10.7754/Clin.Lab.2019.191139

110. Kanda T, Fujii H, Tani T, et al. Intestinal fatty acid-binding protein is a useful diagnostic marker for mesenteric infarction in humans. Gastroenterology. 1996;110(2):339-343. doi:10.1053/gast.1996.v110.pm8566578

111. Thuijls G, van Wijck K, Grootjans J, et al. Early diagnosis of intestinal ischemia using urinary and plasma fatty acid binding proteins. Ann Surg. 2011;253(2):303-308. doi:10.1097/SLA.0b013e318207a767

112. Crenn P, Coudray-Lucas C, Thuillier F, Cynober L, Messing B. Postabsorptive plasma citrulline concentration is a marker of absorptive enterocyte mass and intestinal failure in humans. Gastroenterology. 2000;119(6):1496-1505. doi:10.1053/gast.2000.20227

113. Piton G, Manzon C, Cypriani B, Carbonnel F, Capellier G. Acute intestinal failure in critically ill patients: is plasma citrulline the right marker?. Intensive Care Med. 2011;37(6):911-917. doi:10.1007/s00134-011-2172-x

114. Fragkos KC, Forbes A. Citrulline as a marker of intestinal function and absorption in clinical settings: A systematic review and meta-analysis. United European Gastroenterol J. 2018;6(2):181-191. doi:10.1177/2050640617737632

115. Gondolesi G, Fishbein T, Chehade M, et al. Serum citrulline is a potential marker for rejection of intestinal allografts. Transplant Proc. 2002;34(3):918-920. doi:10.1016/s0041-1345(02)02669-6

116. Ruiz P, Tryphonopoulos P, Island E, et al. Citrulline evaluation in bowel transplantation. Transplant Proc. 2010;42(1):54-56. doi:10.1016/j.transproceed.2009.12.029

117. Herbers AH, Feuth T, Donnelly JP, Blijlevens NM. Citrulline-based assessment score: first choice for measuring and monitoring intestinal failure after high-dose chemotherapy. Ann Oncol. 2010;21(8):1706-1711. doi:10.1093/annonc/mdp596

118. Wedlake L, McGough C, Hackett C, et al. Can biological markers act as non-invasive, sensitive indicators of radiation-induced effects in the gastrointestinal mucosa?. Aliment Pharmacol Ther. 2008;27(10):980-987. doi:10.1111/j.1365-2036.2008.03663.x

119. Altinoz A, Maasher A, Jouhar F, et al. Diagnostic laparoscopy is more accurate than Computerized Tomography for internal hernia after Roux-en-Y gastric bypass. Am J Surg. 2020;220(1):214-216. doi:10.1016/j.amjsurg.2019.10.034

120. Renault K, Gyrtrup HJ, Damgaard K, Hedegaard M, Sørensen JL. Pregnant woman with fatal complication after laparoscopic Roux-en-Y gastric bypass. Acta Obstet Gynecol Scand. 2012;91(7):873-875. doi:10.1111/j.1600-0412.2012.01421.x

121. Marinis A, Yiallourou A, Samanides L, et al. Intussusception of the bowel in adults: a review. World J Gastroenterol. 2009;15(4):407-411. doi:10.3748/wjg.15.407

122. Orthopoulos G, Grant HM, Sharma P, Thompson E, Romanelli JR. S054: incidence and management of jejunojejunal intussusception after Roux-en-Y gastric bypass: a large case series. Surg Endosc. 2020;34(5):2204-2210. doi:10.1007/s00464-019-07009-0

123. Stephenson D, Moon RC, Teixeira AF, Jawad MA. Intussusception after Roux-en-Y gastric bypass. Surg Obes Relat Dis. 2014;10(4):666-670. doi:10.1016/j.soard.2014.01.026

124. Varban O, Ardestani A, Azagury D, et al. Resection or reduction? The dilemma of managing retrograde intussusception after Roux-en-Y gastric bypass. Surg Obes Relat Dis. 2013;9(5):725-730. doi:10.1016/j.soard.2012.05.004

125. Oor JE, Goense L, Wiezer MJ, Derksen WJM. Incidence and treatment of intussusception following Roux-en-Y gastric bypass: a systematic review and meta-analysis. Surg Obes Relat Dis. 2021;17(5):1017-1028. doi:10.1016/j.soard.2021.01.006

126. Patel RA, Brolin RE, Gandhi A. Revisional operations for marginal ulcer after Roux-en-Y gastric bypass. Surg Obes Relat Dis. 2009;5(3):317-322. doi:10.1016/j.soard.2008.10.011

127. Coblijn UK, Goucham AB, Lagarde SM, Kuiken SD, van Wagensveld BA. Development of ulcer disease after Roux-en-Y gastric bypass, incidence, risk factors, and patient presentation: a systematic review. Obes Surg. 2014;24(2):299-309. doi:10.1007/s11695-013-1118-5

128. Dittrich L, Schwenninger MV, Dittrich K, Pratschke J, Aigner F, Raakow J. Marginal ulcers after laparoscopic Roux-en-Y gastric bypass: analysis of the amount of daily and lifetime smoking on postoperative risk. Surg Obes Relat Dis. 2020;16(3):389-396. doi:10.1016/j.soard.2019.11.022

129. Edholm D, Ottosson J, Sundbom M. Importance of pouch size in laparoscopic Roux-en-Y gastric bypass: a cohort study of 14,168 patients. Surg Endosc. 2016;30(5):2011-2015. doi:10.1007/s00464-015-4432-2

130. Carrodeguas L, Szomstein S, Zundel N, Lo Menzo E, Rosenthal R. Gastrojejunal anastomotic strictures following laparoscopic Roux-en-Y gastric bypass surgery: analysis of 1291 patients. Surg Obes Relat Dis. 2006;2(2):92-97. doi:10.1016/j.soard.2005.10.014

131. Ong HI, Robertson J, van Rijnsover M, Booth M. Novel Use of Lumen-Apposing Metal Stent in the Management of Gastrojejunal Stricture Perforation During Endoscopic Dilatation. Obes Surg. 2022;32(9):3213-3214. doi:10.1007/s11695-022-06202-w

132. Wanjura V, Sandblom G, Österberg J, Enochsson L, Ottosson J, Szabo E. Cholecystectomy after gastric bypass-incidence and complications. Surg Obes Relat Dis. 2017;13(6):979-987. doi:10.1016/j.soard.2016.12.004

133. Jonas E, Marsk R, Rasmussen F, Freedman J. Incidence of postoperative gallstone disease after antiobesity surgery: population-based study from Sweden. Surg Obes Relat Dis. 2010;6(1):54-58. doi:10.1016/j.soard.2009.03.221

134. Melmer A, Sturm W, Kuhnert B, et al. Incidence of Gallstone Formation and Cholecystectomy 10 Years After Bariatric Surgery. Obes Surg. 2015;25(7):1171-1176. doi:10.1007/s11695-014-1529-y

135. Collins C, Maguire D, Ireland A, Fitzgerald E, O'Sullivan GC. A prospective study of common bile duct calculi in patients undergoing laparoscopic cholecystectomy: natural history of choledocholithiasis revisited. Ann Surg. 2004;239(1):28-33. doi:10.1097/01.sla.0000103069.00170.9c

136. The Swedish Registry of Gallstone Surgery and Endoscopic Retrograde Cholangiopancreatography (GallRiks):– Årsrapport 2016, p.30 https://www.ucr.uu.se/gallriks/for-vardgivare/rapporter/arsrapporter/arsrapport-2016/viewdocument/408

Published August 8th, 2017, Accessed September 12th, 2022.

137. Peters M, Papasavas PK, Caushaj PF, Kania RJ, Gagné DJ. Laparoscopic transgastric endoscopic retrograde cholangiopancreatography for benign common bile duct stricture after Roux-en-Y gastric bypass. Surg Endosc. 2002;16(7):1106. doi:10.1007/s00464-001-4180-3

138. Aiolfi A, Asti E, Rausa E, Bernardi D, Bonitta G, Bonavina L. Trans-Gastric ERCP After Roux-en-Y Gastric Bypass: Systematic Review and Meta-Analysis. Obes Surg. 2018;28(9):2836-2843. doi:10.1007/s11695-018-3258-0

139. Frederiksen NA, Tveskov L, Helgstrand F, Naver L, Floyd A. Treatment of Common Bile Duct Stones in Gastric Bypass Patients with Laparoscopic Transgastric Endoscopic Retrograde Cholangiopancreatography. Obes Surg. 2017;27(6):1409-1413. doi:10.1007/s11695-016-2524-2

140. Banerjee N, Parepally M, Byrne TK, Pullatt RC, Cote GA, Elmunzer BJ. Systematic review of transgastric ERCP in Roux-enY gastric bypass patients. Surg Obes Relat Dis. 2017;13(7):1236- 42. doi.org/10.1016/j.soard.2017.02.005.

141. Borel F, Branche J, Baud G, Gérard R, Pattou F, Caiazzo R. Management of Acute Gallstone Cholangitis after Roux-en-Y Gastric Bypass with Laparoscopic Transgastric Endoscopic Retrograde Cholangiopancreatography. Obes Surg. 2019;29(2):747-748. doi:10.1007/s11695-018-3620-2

142. Lopes TL, Clements RH, Wilcox CM. Laparoscopy-assisted ERCP: experience of a high-volume bariatric surgery center (with video). Gastrointest Endosc. 2009;70(6):1254-1259. doi:10.1016/j.gie.2009.07.035

143. Liljegard S, Fredriksson Å, Manke T, Kylebäck A, Larsson PA, Haraldsson E. The Outcome of Laparoscopy-Assisted Transgastric Rendezvous ERCP During Cholecystectomy After Roux-en-Y Gastric Bypass Compared to Normal Controls [published online ahead of print, 2022 Aug 29]. Obes Surg. 2022;10.1007/s11695-022-06246-y. doi:10.1007/s11695-022-06246-y

144. Phillips EH, Carroll BJ, Pearlstein AR, Daykhovsky L, Fallas MJ. Laparoscopic choledochoscopy and extraction of common bile duct stones. World J Surg. 1993;17(1):22-28. doi:10.1007/BF01655700

145. Petelin JB. Laparoscopic common bile duct exploration. Surg Endosc. 2003;17(11):1705-1715. doi:10.1007/s00464-002-8917-4

146. Lyass S, Phillips EH. Laparoscopic transcystic duct common bile duct exploration. Surg Endosc. 2006;20 Suppl 2:S441-S445. doi:10.1007/s00464-006-0029-0

147. Nassar AHM, Ng HJ, Katbeh T, Cannings E. Conventional Surgical Management of Bile Duct Stones: A Service Model and Outcomes of 1318 Laparoscopic Explorations. Ann Surg. 2022;276(5):e493-e501. doi:10.1097/SLA.0000000000004680

148. Petersson U, Johansen D, Montgomery A. Laparoscopic transcystic laser lithotripsy for common bile duct stone clearance. Surg Laparosc Endosc Percutan Tech. 2015;25(1):33-36. doi:10.1097/SLE.0b013e31829cec5d

149. Reinders JS, Gouma DJ, Ubbink DT, van Ramshorst B, Boerma D. Transcystic or transductal stone extraction during single-stage treatment of choledochocystolithiasis: a systematic review. World J Surg. 2014;38(9):2403-2411. doi:10.1007/s00268-014-2537-8

150. Fisher, Ronald A. (1971) [1935]. The Design of Experiments (9th ed.). Macmillan. ISBN 0-02-844690-9.

151. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240(2):205-213. doi:10.1097/01.sla.0000133083.54934.ae

152. Bruze G, Ottosson J, Neovius M, Näslund I, Marsk R. Hospital admission after gastric bypass: a nationwide cohort study with up to 6 years follow-up. Surg Obes Relat Dis. 2017;13(6):962-969. doi:10.1016/j.soard.2017.01.004

153. van Olst N, van Rijswijk AS, Mikdad S, et al. Long-term Emergency Department Visits and Readmissions After Laparoscopic Roux-en-Y Gastric Bypass: a Systematic Review. Obes Surg. 2021;31(6):2380-2390. doi:10.1007/s11695-021-05286-0

154. Mala T, Høgestøl I. Abdominal Pain After Roux-En-Y Gastric Bypass for Morbid Obesity. Scand J Surg. 2018;107(4):277-284. doi:10.1177/1457496918772360

155. Høgestøl IK, Chahal-Kummen M, Eribe I, et al. Chronic Abdominal Pain and Symptoms 5 Years After Gastric Bypass for Morbid Obesity. Obes Surg. 2017;27(6):1438-1445. doi:10.1007/s11695-016-2499-z

156. Sandvik J, Hole T, Klöckner CA, Kulseng BE, Wibe A. High-Frequency of Computer Tomography and Surgery for Abdominal Pain After Roux-en-Y Gastric Bypass. Obes Surg. 2018;28(9):2609-2616. doi:10.1007/s11695-018-3223-y

157. Wu TH, Huang GS, Wu CT, Lai JY, Chen CC, Hu MH. Clinical characteristics of pediatric intussusception and predictors of bowel resection in affected patients. Front Surg. 2022;9:926089. Published 2022 Aug 30. doi:10.3389/fsurg.2022.926089

158. Möller M, Gustafsson U, Rasmussen F, Persson G, Thorell A. Natural course vs interventions to clear common bile duct stones: data from the Swedish Registry for Gallstone Surgery and Endoscopic Retrograde Cholangiopancreatography (GallRiks). JAMA Surg. 2014;149(10):1008-1013. doi:10.1001/jamasurg.2014.249

159. Durán M, Silvestre J, Hernández J, Briceño J, Martínez-Isla A, Martínez-Cecilia D. Learning curve for performing laparoscopic common bile duct exploration in biliary surgery 2.0 era [published online ahead of print, 2022 Aug 10]. J Hepatobiliary Pancreat Sci. 2022;10.1002/jhbp.1228. doi:10.1002/jhbp.1228

160. Hedenbro JL, Näslund E, Boman L, et al. Formation of the Scandinavian Obesity Surgery Registry, SOReg. Obes Surg. 2015;25(10):1893-1900. doi:10.1007/s11695-015-1619-5

161. Sundbom M, Näslund I, Näslund E, Ottosson J. High acquisition rate and internal validity in the Scandinavian Obesity Surgery Registry. Surg Obes Relat Dis. 2021;17(3):606-614. doi:10.1016/j.soard.2020.10.017Rystedt J, Montgomery A, Persson G. Completeness and correctness of cholecystectomy data in a national register-GallRiks. Scand J Surg 2014; 103: 237–244. doi:10.1177/1457496914523412

162. Rystedt J, Montgomery A, Persson G. Completeness and correctness of cholecystectomy data in a national register-GallRiks. Scand J Surg 2014; 103: 237–244. doi:10.1177/1457496914523412

163. Rystedt J, Lindell G, Montgomery A. Bile Duct Injuries Associated With 55,134 Cholecystectomies: Treatment and Outcome from a National Perspective. World J Surg 2016; 40: 73–80. doi:10.1007/s00268-015-3281-4

Appendix

Supplementary table 1. Readmissions and surgeries during follow-up period in relation to diagnosis at first admission surgery or discharge.

			Diagnosis at surgery									Diagnosis without surgery					
			Surgery for RYGB complication						Other surgeries								
		Early admissions[1]	Internal herniation	Obstruction at jejunojejunostomy	Jejuno-jejunal intussusception	Small bowel obstruction	Perforation	Incisional hernia	Gallstone disease	Miscellaneous	Unremarkable laparoscopy	Unspecified abdominal pain	Gallstone disease	Other specific disease	All operated patients	All non-operated patients	*p* value
Patients n (%)		18	42	4	2	9	6	3	23	9	30	100	14	20	128	134	
		(6)	(15)	(1)	(1)	(3)	(2)	(1)	(8)	(3)	(11)	(36)	(5)	(7)	(46)	(51)	
Average follow-up time (months) Mean		58.3	60.4	63.3	51.5	60.8	54.7	68	57.2	52.4	58.2	59.5	54.7	55.9	58.6	58.4	.845
Readmission n (%)	< 30 days	3	2	0	0	0	0	1	2	1	1	14	2	0	7	16	.064
		(17)	(5)					(33)	(9)	(11)	(3)	(14)	(14)		(6)	(12)	
	within follow-up period[2]	8	14	2	0	2	3	2	9	2	14	44	5	9	48	58	.340
		(44)	(33)	(50)		(22)	(50)	(67)	(33)	(22)	(47)	(44)	(36)	(45)	(38)	(43)	
Surgery at a later admission n (%)	RYGB complication	2	8	2	0	1	1	1	2	0	5	19	0	3	20	22	.861
		(11)	(19)	(50)		(11)	(17)	(33)	(9)		(17)	(19)		(15)	(16)	(16)	
	Internal herniation	0	4	0	0	0	0	1	1	0	2	9	0	1	8	10	.698
			(10)					(33)	(4)		(7)	(9)		(5)	(6)	(8)	
	Other surgery	3	4	0	0	0	0	1	2	1	3	14	3	0	11	17	.284
		(17)	(10)					(33)	(9)	(11)	(10)	(14)	(21)		(9)	(13)	

Categorical variables are presented as frequency (percentage) and average follow-up time is presented as mean. Values are rounded to nearest whole number, while median is presented to one decimal place. *p* values are calculated using Mann-Whitney non-parametric test or Pearson's Chi-Square test comparing operated to non-operated patients.

[1] Represents all early admissions (≤30 days after RYGB) operated or non-operated. [2] Until 17th October 2018