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TREATMENT OF CHOLELITHIASIS AND ACUTE CHOLECYSTITIS

SURGICAL SAFETY IN GALLSTONE SURGERY

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Treatment of Cholelithiasis and Acute Cholecystitis

Surgical Safety in Gallstone Surgery

Thesis for Doctoral Degree (Ph.D.)

By

My Blohm

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To Céline, Alphons and Damien

"Creativity is intelligence having fun."

Albert Einstein

FOREWORD

You are reading a thesis about gallstone surgery, one of the most common surgical procedures in the world. In this book, I will guide you through the background and available evidence about gallstone disease and its most common complication, gallbladder inflammation. A thesis also brings new evidence to the research field. This thesis includes five research papers in which my colleagues and I have invested time, thoughts and sometimes frustration. Three studies are registry-based cohort studies; one is an observational learning-curve study, and the last one is a randomized controlled trial. They all have different focal points, with at least one important thing in common: they all focus on different aspects of surgical safety in gallstone surgery.

While reading, you will also get an insight into a seven-year long research journey, and my development as a researcher. The first paper was a scientific project during my residency in general surgery. It was also the stepping stone to my PhD studies. Apart from the first study, where my supervisors were actively involved, I have conducted the studies in this thesis independently, under supervision. I have learned to design and conduct registry-based and multicentre studies, performed different statistical analyses, written and edited manuscripts and finally felt relieved, and happy, when they have been accepted for publication.

Research has become both an interest and a source for intellectual stimulation, but I am also a clinician. I have spent the clinical part of these seven years at Mora Lasarett, a county hospital in the middle of Sweden. These years of research also include my clinical development, extending from the first years of surgical residency, finishing as a specialist. I have had the opportunity to operate with, and learn from, some of the most experienced gallstone surgeons in Sweden. Some clinical thoughts and experiences will also be shared here. This thesis is the result of this academic and clinical journey.

My wish is that after finishing reading, you will feel updated about the existing evidence about the gallstone disease; that you will get an insight into my contribution to this vast field of research and hopefully also feel inspired to embark on a new research journey, perhaps in collaboration.

My Blohm

Mora, October 28, 2023

POPULAR SCIENCE SUMMARY

The presence of stones in the gallbladder, cholecystolithiasis, is common, and around ten to fifteen percent of the general population have gallstones. The stones can have different shapes and structures. They can be one or one hundred; big, small or a mixture of different sizes. Most stones do not cause problems, but they can result in pain attacks or an acute inflammation of the gallbladder, an acute cholecystitis. Patients with frequent pain attacks or acute cholecystitis are common visitors to emergency departments. Research on gallstone disease is important because it has the potential to improve healthcare for many patients, worldwide. The treatment for recurrent pain attacks or acute cholecystitis is surgical removal of the gallbladder. This is usually done with key-hole surgery (laparoscopic cholecystectomy). This operation is an important cornerstone of surgical education, and most surgeons preform it at some point during their career. A cholecystectomy can be a simple surgical procedure, but variations in anatomy and the level of inflammation can increase the difficulty. Complications occur in more than one tenth of all operations and, therefore, increasing surgical safety in gallstone surgery is highly relevant. This thesis includes five different research papers, all focussing on various aspects of surgical safety in gallstone surgery. The studies included are described briefly below. To some extent, all these studies are based on the Swedish National Registry of Gallstone Surgery, called GallRiks. Five research questions summarize the content of this thesis.

PAPER 1 – *When is the optimal timing of surgery for patients with acute cholecystitis?*

The aim of the first study was to analyse whether the timing of surgery for acute cholecystitis affects the complication rate. The study used data from GallRiks from 2006 to 2014. In total, 15,760 patients with acute cholecystitis were included. The patients were divided into six groups depending on when they underwent surgery. Of these, 12% underwent surgery on the day of admission; 39% on the first day in hospital and 27% on the second day. When comparing the results from each day with the highest group (≥ 5 days), we found that patients undergoing surgery on day one or two had the lowest complication rates. The conclusion is that the optimal timing of surgery seems to be within two days of hospital admission.

PAPER 2 – *Does the operative volume of cholecystectomies impact surgical outcomes?*

The aim of this study was to investigate whether the surgeon's and hospital's annual volume of cholecystectomies have an impact on complication rates and operating times. The study used data from GallRiks from 2006 to 2019. All patients undergoing cholecystectomy were included, whether as a result of pain attacks or complications. We analysed 154,934 patients. The hospital's and surgeon's annual volumes were calculated from the total number of operations performed the year before each operation. The procedures were divided into four volume-based groups. When comparing operating times and complications between the groups, we found that hospitals and surgeons with low volumes had worse results. The conclusion is that hospital and surgeon volumes influence outcomes in cholecystectomy.

PAPER 3 – *Do female and male surgeons' outcomes differ in cholecystectomy?*

The aim of this study was to analyse whether female and male surgeons differ in operating time and complications in planned and acute cholecystectomies. The study used data from GallRiks from 2006 to 2019. A total of 150,509 patients were included. When comparing differences between female and male surgeons, we found that female surgeons had longer operation times, but their patients had fewer complications, and shorter hospital stays. The conclusion is that female surgeons seem to have more favourable outcomes but operate more slowly than male surgeons, in both planned and acute cholecystectomies.

PAPER 4 – *Is ultrasonic fundus-first dissection easy and safe during the learning curve?*

The aim of this study was to evaluate the learning curve for an alternative surgical technique used for dissection, in planned laparoscopic cholecystectomy. The technique is called ultrasonic fundus-first dissection. Surgeons with no previous experience of the technique could participate. All surgeons were experienced with cholecystectomy with the traditional technique, called electrocautery dissection. Patients were recruited from 2017 to 2019. Sixteen surgeons performed 15 operations each, and 240 patients were included. The data collected in the study were complemented with information from GallRiks. Operating times and complication rates were analysed. In addition, five of the procedures were recorded and the videos were graded by two external surgeons. The results showed that dissection time decreased during the learning curve. The technique had a low complication rate, comparable to the traditional technique. The conclusion is that ultrasonic-fundus first dissection is easy to learn and safe during the learning curve.

PAPER 5 – *Is ultrasonic or electrocautery dissection preferable in acute cholecystitis?*

The aim of this study was to investigate whether ultrasonic dissection might be an alternative to traditional electrocautery dissection in patients with acute cholecystitis. The study was designed as a randomized controlled trial, meaning that patients with acute cholecystitis were randomly assigned to either electrocautery dissection or ultrasonic dissection. Patients were recruited from 2019 to 2023. A total of 300 patients were included, of whom 148 were assigned to electrocautery dissection and 152 to ultrasonic dissection. Neither the patients nor postoperative caregivers knew which technique was used. The data collected within the study were complemented with information from GallRiks. In addition, laboratory tests were performed before and after surgery, and the patients graded their level of pain and nausea in a diary before surgery and during the first seven days postoperatively. The results showed that the total amount of complications was the same in both groups. The surgeons used fewer additional products to stop bleeding with ultrasonic dissection and this technique might be especially useful in complicated cases. The conclusion is that ultrasonic dissection is a safe alternative to electrocautery dissection in patients with acute cholecystitis.

POPULÄRVETENSKAPLIG SAMMANFATTNING

BAKGRUND

Gallstenar i gallblåsan, kolecystolithiasis, är vanligt och förekomsten ökar med åldern. I de flesta fall ger stenarna inga besvär men de kan blockera flödet av galla från gallblåsan till tarmen, vilket kan ge intensiva smärtor. Stenarna kan också orsaka en gallblåseinflammation, akut kolecystit. Vid återkommande gallstenssmärtor och akut kolecystit rekommenderas kirurgiskt borttagande av gallblåsan. Det sker nästintill alltid med titthålskirurgi. Inom kirurgin benämns operationen laparoskopisk kolecystektomi. Operationen är ett av de vanligaste allmänkirurgiska ingrepp som utförs i Sverige och världen, och är ofta relativt okomplicerad. En gallblåseinflammation och andra faktorer kan dock öka svårighetsgraden avsevärt och komplikationer förekommer så ofta som i en tiondel av operationerna. Det finns därför mycket att vinna på att öka den kirurgiska säkerheten. Den här avhandlingen innehåller fem forskningsstudier som alla fokuserar på olika aspekter av kirurgisk säkerhet inom gallkirurgi. Alla studier baseras i någon utsträckning på det svenska nationella kvalitetsregistret för gallstenskirurgi, GallRiks. Avhandlingens delstudier kan sammanfattas i fem frågor och presenteras i korthet här nedan.

DELARBETE 1 – *När är det optimalt att operera en patient med akut kolecystit?*

Studiens syfte var att analysera hur tidpunkten för kirurgi vid akut kolecystit påverkar andelen komplikationer. Studien var baserad på data från GallRiks, 2006 till 2014. Totalt 15 760 patienter med akut kolecystit analyserades. Patienterna delades in i sex grupper beroende på vilken dag de opererades. Av de inkluderade patienterna opererades 12 procent på ankomstdagen, 39 procent första dagen och 27 procent andra dagen efter inskrivning på sjukhus. Skillnaden i komplikationsfrekvens analyserades för de olika grupperna, i relation till referensgruppen (≥ 5 dagar). Resultaten visade att patienter som opererades första eller andra dygnet hade lägst andel komplikationer. Slutsatsen är att den optimala tidpunkten att operera en patient med akut kolecystit är inom två dygn efter inskrivning.

DELARBETE 2 – *Påverkar operationsvolymen resultaten vid gallkirurgi?*

Studiens syfte var att analysera om sjukhusets och kirurgens volym av gallkirurgi påverkar antalet komplikationer och operationstiden. Studien var baserad på data från GallRiks. Alla patienter som genomgått gallblåsekirurgi mellan 2006 och 2019, på grund av gallstenssmärta eller gallblåseinflammation, inkluderades i studien. Totalt 154 934 patienter analyserades. Operationsvolymerna beräknades utifrån antalet galloperationer som utförts året innan varje operation. Operationerna delades därefter in i fyra volymbaserade grupper, som jämfördes avseende komplikationer och operationstid. Resultaten visade att lågvolymssjukhus och lågvolymskirurger hade högre andel komplikationer och längre operationstider. Slutsatsen är att operationsvolymen påverkar resultaten vid gallkirurgi.

DELARBETE 3 – *Har kvinnliga och manliga kirurger olika resultat vid gallkirurgi?*

Studiens syfte var att analysera om kvinnliga och manliga kirurger skiljer sig åt vad gäller komplikationer och operationstid vid planerad och akut gallkirurgi. Studien var baserad på data från GallRiks, 2006 till 2019. Totalt inkluderades 150 509 operationer som analyserades avseende skillnader i resultat mellan kvinnliga och manliga kirurger. Resultaten visade att kvinnliga kirurger opererade lite långsammare men deras patienter hade färre komplikationer och kortare vårdtider. Slutsatsen är att kvinnliga kirurger har mer fördelaktiga resultat men opererar något långsammare vid både planerad och akut gallkirurgi.

DELARBETE 4 – *Är gallkirurgi med ultraljudsdissektion enligt fundus-first lätt att lära sig och säker under inlärningskurvan?*

Studiens syfte var att utvärdera inlärningskurvan för en alternativ kirurgisk teknik som används för dissektion av gallblåsan. Tekniken kallas för ultraljudsdissektion enligt fundus-first, det vill säga att gallblåsan löses från toppen och nedåt med ett ultraljudsinstrument. Studien omfattade kirurger med erfarenhet av den traditionella metoden med diatermidissektion, men utan erfarenhet av ultraljudsdissektion vid gallkirurgi. Patienter som opererades mellan 2017 och 2019 kunde inkluderas i studien. Sexton kirurger utförde vardera femton planerade kolecystektomier, totalt 240 operationer. Studiedata kompletterades med data från GallRiks. Tiden för dissektionen och komplikationsfrekvensen analyserades under inlärningskurvan. Utöver detta bedömdes fem operationsfilmer av två externa granskare med stor erfarenhet av tekniken. Resultaten visade att dissektionstiden blev kortare under inlärningskurvan. Komplikationsfrekvensen var jämförbar med vad som rapporteras i GallRiks för den traditionella tekniken. Slutsatsen är att tekniken med ultraljudsdissektion enligt fundus-first är lätt att lära sig och säker under inlärningskurvan vid planerad gallkirurgi.

DELARBETE 5 – *Är ultraljudsdissektion eller diatermi mest fördelaktigt för patienter med akut kolecystit?*

Studiens syfte var att studera om ultraljudsdissektion är ett mer fördelaktigt alternativ till traditionell diatermidissektion, vid operation av patienter med akut kolecystit. Studien var designad som en randomiserad kontrollerad studie, vilket innebär att patienter med akut kolecystit blev slumpmässigt fördelade till gallkirurgi med antingen diatermi- eller ultraljudsdissektion. Studien pågick mellan 2019 och 2023. Totalt 300 patienter opererades, 148 med diatermikrok och 152 med ultraljudsdissektion. Kirurgen kunde själv välja dissektionsriktning. Patienterna och uppföljande personal fick inte veta vilket instrument som använts under operationen. Labprover togs innan och efter operationen. Patienterna fick gradera sin smärta och illamående i en patientdagbok innan och de första sju dagarna efter operationen. Studiedata kompletterades med data från GallRiks. Resultaten visade att komplikationsfrekvensen för de båda instrumenten var jämförbar. Kirurgerna använde mindre ofta blodstillande produkter vid ultraljudsdissektion, vilket talar för att tekniken är speciellt användbar i mer komplicerade inflammationer. Slutsatsen är att ultraljudsdissektion är ett säkert alternativ till diatermidissektion vid operation av patienter med akut kolecystit.

ABSTRACT

INTRODUCTION

Laparoscopic cholecystectomy is one of the most frequently performed surgical procedures worldwide, with nearly 14,000 operations per year in Sweden alone. Recurrent biliary colic or acute cholecystitis are indications for surgery. Despite being a standardized procedure, complications occur in more than 10% of all operations. This thesis includes five research papers, all of which focus on different aspects of surgical safety in gallstone surgery.

PAPER 1

The recommended treatment of acute cholecystitis is acute cholecystectomy during the first hospital admission, but the optimal timing is still under discussion. The aim of the first study was to analyse whether the timing of surgery for acute cholecystitis affects complication rates. A registry-based study, based on the Swedish National Registry for Gallstone Surgery and Endoscopic Retrograde Pancreatography (GallRiks) was performed. We included 87,108 patients undergoing cholecystectomy from 2006 to 2014. Of these operations, 15,760 (18.1%) were performed due to acute cholecystitis. We analysed differences in outcomes related to timing of surgery. The results showed that intra-and postoperative complications, bile duct injuries and 30-and 90-day mortality increased with longer delays. The conclusion is that the optimal timing of surgery seems to be within two days of hospital admission.

PAPER 2

Increasing hospital and surgeon volumes have been associated with better outcomes for more complicated procedures. However, it is still unknown whether the annual volume of cholecystectomies affects surgical outcomes. The aim of this study was to investigate whether the surgeon's and hospital's annual volume of cholecystectomies has an impact on complication rates and operating time. A registry-based study was conducted based on all cholecystectomies registered in GallRiks between 2006 and 2019. A total of 154,934 patients were analysed: 101,221 (65.3%) elective procedures and 53,713 (34.7%) acute procedures. Low volume was defined as <211 operations per hospital per year and <20 operations per surgeon per year. The correlation between annual volumes and different outcomes was calculated. The conclusion is that high volume hospitals and surgeons have more favourable outcomes in both elective and acute cholecystectomy.

PAPER 3

Female and male physicians practice medicine differently but it is still unknown whether female and male surgeons produce different outcomes. The aim of this study was to analyse whether female and male surgeons differ in complication rates and operating times in both elective and acute cholecystectomies. A registry-based study was performed based on all cholecystectomies registered in GallRiks between 2006 and 2019. In total, 150,509 patents were included: 97,755 (64.9%) were elective and 52,754 (35.1%) were acute operations. Procedures were performed by 2,553 surgeons: 849 (33.3%) female surgeons and 1,704 (67.7%) male surgeons. Differences in outcomes and operating times were analysed. The results showed that patients operated on by male

surgeons had more surgical complications overall (Odds Ratio (OR) 1.29, 95% CI 1.19-1.40) including more bile duct injures in elective surgery (OR 1.69, 95% CI 1.22-2.34). In addition, female surgeons had longer operating times; converted less frequently to open surgery in the acute setting and their patients had overall shorter hospital stays. The conclusion is that female surgeons have more favourable outcomes but operate more slowly than male surgeons, in elective and acute cholecystectomies.

PAPER 4
An alternative to electrocautery dissection is ultrasonic dissection, which has proven favourable in elective cholecystectomies. The aim of this study was to evaluate the learning curve for ultrasonic fundus-first dissection, in elective laparoscopic cholecystectomy. Surgeons with no previous experience of the technique could participate. Patients were recruited between 2017 and 2019. Sixteen residents and specialists, from eight Swedish hospitals, performed 15 operations each and 240 patients were included. The primary endpoint was dissection time with secondary endpoints being complication rate and the surgeon's self-assessed performance level. In addition, five of the operations were recorded and the videos were graded by two external surgeons. Associations between the procedural number and the different outcomes were analysed. The results showed that dissection time decreased as experience increased (p=0.001). The technique had a complication rate of 5.8%, comparable to the traditional technique. No correlation between the number of performed procedures and the video-assessment score could be demonstrated. The self-assessed performance level was rated lower in more complicated procedures (p=<0.001). The conclusion is that ultrasonic fundus-first dissection is easy to learn and safe during the learning curve, for both residents and specialists.

PAPER 5
Ultrasonic dissection seems to be a safe alternative in elective cholecystectomy, but it is still unclear whether the technique is favourable in acute operations. The aim of this study was to compare electrocautery to ultrasonic dissection in patients with acute cholecystitis. A multicentre, randomized, controlled trial was conducted at eight Swedish hospitals. Eligible participants were patients ≥18 years old, with acute cholecystitis with a duration of ≤7 days. Patients were randomly assigned to either traditional electrocautery or ultrasonic dissection, with a 1:1 allocation. Patients, postoperative caregivers, and follow-up personnel were masked to group assignment. The primary endpoint was the total complication rate with analyses according to intention-to-treat. From September 30, 2019, until March 22, 2023, a total of 300 patients was randomized to electrocautery dissection (n=148) or ultrasonic dissection (n=152). No difference in complication rate was seen between the groups (risk difference (RD) 1.6%, 95% CI - 7.2% to 10.4%, p=0.72). Haemostatic agents were used in 40 (27.0%) of patients assigned to electrocautery and 27 (17.8%) of patients assigned to ultrasonic dissection, (RD 10.6%, 95% CI 1.3%-19.8%, p=0.025). In 13 (8.8%) operations in the electrocautery group the surgeon chose to use ultrasonic dissection mostly due to the perceived higher complexity of the operation. The conclusion is that ultrasonic and electrocautery dissection have comparable risks for total complications in patients with acute cholecystitis. Ultrasonic dissection can be used as an alternative to electrocautery dissection, or as a complement in complicated cases.

LIST OF SCIENTIFIC PAPERS

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals.

I. **The Sooner, the Better? The importance of Optimal Timing of Cholecystectomy in Acute Cholecystitis: Data from the National Swedish Registry for Gallstone Surgery, GallRiks**

My Blohm, Johanna Österberg, Gabriel Sandblom, Lars Lundell, Mats Hedberg and Lars Enochsson

J Gastrointest Surg. 2017;21(1):33-40

II. **Relationship between surgical volume and outcomes in elective and acute cholecystectomy: nationwide, observational study**

My Blohm, Gabriel Sandblom, Lars Enochsson, Mats Hedberg, Mikael Andersson Franko, Johanna Österberg

Br J Surg. 2023;110(3):353-61.

III. **Differences in Cholecystectomy Outcomes and Operating Time Between Male and Female Surgeons in Sweden**

My Blohm, Gabriel Sandblom, Lars Enochsson, Johanna Österberg

JAMA surgery. Published online August 30, 2023

IV. **Learning by doing: an observational study of the learning curve for ultrasonic fundus-first dissection in elective cholecystectomy**

My Blohm, Gabriel Sandblom, Lars Enochsson, Yücel Cengiz, Edmunds Austrums, Elisabeth Abdon, Joakim Hennings, Mats Hedberg, Ulf Gustafsson, Angelica Diaz-Pannes, Johanna Österberg

Surg Endosc. 2022;36(6):4602-13

V. **Ultrasonic dissection in laparoscopic cholecystectomy for acute cholecystitis, a randomized controlled trial**

My Blohm, Gabriel Sandblom, Lars Enochsson, Yücel Cengiz, Haytham Bayadsi, Joakim Hennings, Erik Stenberg, Johanna Österberg

Manuscript

LIST OF ABBREVIATIONS

ASA	American Society of Anesthesiologists Physical Status Classification
AC	Acute Cholecystitis
BMI	Body Mass Index
CBDS	Common Bile Duct Stones
CI	Confindence Interval
CONSORT	Guidelines used for reporting parallel group randomized trials
CRF	Case Report Form
CRP	C-Reactive Protein
CT	Computed Tomography
CVS	Critical View Of Safety
eCRF	Electronic Case Report Form
ERCP	Endoscopic Retrograde Cholangiopancreatography
FF	Fundus-First
GallRiks	Swedish Registry for Gallstone Surgery and Endoscopic Retrograde Cholangiopancreatography
GEE	Generalized Estimating Equations
IQR	Interquartile Range
LEFFE	Learning Curve of Ultrasonic Fundus-First Dissection, our running title for PAPER IV
LOS	Length of Stay
MRI	Magnetic Resonance Imaging
NSAID	Nonsteroidal Anti-Inflammatory Drug
OR	Odds Ratio
PROM	Patient-Reported Outcome Measures
RCT	Randomized Controlled Trial
RRCT	Registry-Based Randomized Controlled Trial
RD	Risk Difference
SD	Standard Deviation
SONOCHOL	Our running title for PAPER V
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology: guidelines for observational studies
QoL	Quality of Life
WBC	White Blood Cells

CONTENTS

TREATMENT OF CHOLELITHIASIS AND ACUTE CHOLECYSTITIS			
STUDY	**RESEARCH QUESTION**	**STUDY DESIGN**	**MAIN FINDING**
PAPER I The sooner the better	When is the optimal timing of surgery for patients with acute cholecystitis?	Population-based cohort study, including 87,108 cholecystectomies from 2006 to 2014.	The optimal timing of surgery for patients with acute cholecystitis seems to be within two days of hospital admission.
PAPER II Case Volume	Does the operative volume of cholecystectomies impact surgical outcomes?	Population-based cohort study, including 154,934 cholecystectomies from, 2006 to 2019	Hospital and surgeon volumes influence outcomes in cholecystectomy.
PAPER III Gender in Surgery	Do female and male surgeons' outcomes differ in cholecystectomy?	Population-based cohort study, including 150,509 cholecystectomies from 2006 to 2019	Female surgeons have more favourable outcomes and operate more slowly than male surgeons in cholecystectomy.
PAPER IV LEFFE	Is ultrasonic fundus-first dissection easy and safe during the learning curve?	Clinical observational study, including 16 surgeons, performing 240 cholecystectomies from 2017 to 2019.	Ultrasonic fundus-first dissection is easy to learn and safe during the learning curve.
PAPER V SONOCHOL	Is ultrasonic or electrocautery dissection preferable in acute cholecystitis?	Randomized controlled trial, including 300 patients with acute cholecystitis, from 2019 to 2023.	There is no difference in complication rates between ultrasonic and electrocautery dissection in acute cholecystitis.

1 LITERATURE REVIEW

1.1 MY FRIEND ARNE

Arne is 75 years old. He has high blood-pressure and is slightly overweight. Most of the time, he is happy and still curious about the future. His bookshelves are loaded with scientific and political literature, a way to find stimulation after a long working life as an engineer. It is Sunday afternoon in his calm apartment when his symptoms begin. Half an hour after dinner his stomach becomes upset. It aches, and rumbles. Despite some time on the sofa bed, the pain persists. Arne tries to sleep but wakes up several times during the night. In the morning, the general aching has moved to the upper right part of his abdomen. His belly feels distended, and he feels more than slightly overweight. His habitual, irritating cough makes the pain even worse. After some reflection and agony, he decides to drive to the local hospital. He waits for hours in the emergency department. The pain gets worse, and he starts to feel feverish. After several hours, a young doctor comes and examines him: *Is this the first time you have felt like this?* He suddenly recalls a disastrous Midsummer celebration two years ago with intense pain after eating the traditional herring, but this long-lasting sensation is new. The doctor thinks that Arne might have a gallbladder inflammation and suggests doing an ultrasound. He waits, he waits for hours. After the ultrasound another doctor comes and explains that Arne has an inflamed gallbladder which must be removed by surgery. He gets a bed at the hospital, and he waits, this time for two days. When it is time for surgery, he can hardly remember his earlier, happy days. Hungry, almost angry, he agrees to take part in a study about two different surgical instruments. They want to test whether a new instrument might be better for him. "Why not?" he asks himself. "Perhaps it can improve hospital care for someone else." Luckily, the operating team seems experienced, and the female doctor is nice and friendly. When he wakes up after the operation, he is tired, but the pain is less intense. He feels more like himself and starts to plan for his Monday bridge session. When he meets the surgeon the next morning, he has a paper by his side. On the paper he has written five questions. He asks:

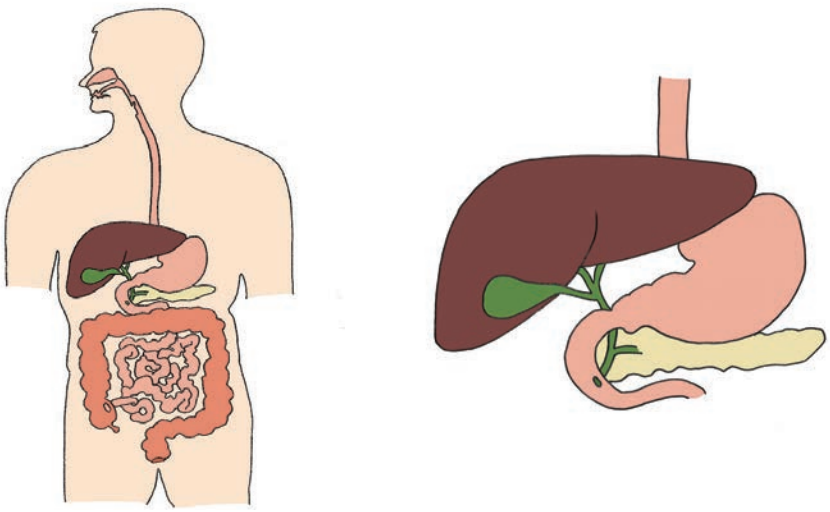
- Why did you wait so long before operating?
- Do you perform a lot of gallstone operations at this hospital?
- Is it unusual to be a female surgeon performing gallstone surgery?
- Was it difficult to learn how to use the new instrument in the study?
- Which instrument do you think is best for patients like me, with gallbladder inflammation?

I told Arne that I hope to be able to answer his questions in this thesis.

1.2 CHOLELITHIASIS – THE GALLSTONE DISEASE

1.2.1 Physiology at a glance

The gallbladder contains bile and is attached to the liver, under the diaphragm in the upper right quadrant of the abdomen. Bile has two major functions. It enables the digestion and absorption of lipids from the intestines, and it is a medium for the liver to excrete redundant cholesterol, bilirubin, copper and iron [1]. Bile is composed of water (>90%), phospholipids, cholesterol, bile salts, bile pigments and electrolytes [2]. It is produced continuously by the liver and stored and concentrated in the gallbladder.



Figures 1.2.1 Anatomical overview of the gallbladder

1.2.2 Pathophysiology – gallstone formation

The main component in most gallstones, at least in western countries, is cholesterol [2]. Cholesterol stones are formed as the result of an imbalance in bile secretion and cholesterol elimination. Gallstone formation can result from hypersecretion of cholesterol in metabolic disorders, inadequate secretion of bile salts, excess gallbladder mucin, and altered gallbladder and intestinal motility [1]. Apart from the most common cholesterol stones, haemolytic disorders, bile duct obstruction, stasis and bacterial growth can result in the formation of brown or black pigment stones [3, 4]. There can be just one gallstone or hundreds, and gallstones can occur in many different shapes.

1.2.3 Epidemiology

Even today, the exact prevalence of gallstones is difficult to assess. Studies based on autopsies or surgery, as well as more recently performed ultrasound studies, tend to reflect only selected groups of the population. Overall prevalence varies from 5% to 25%, with significant geographical variations [5-9]. In Sweden, prevalence might be as high as 20%, and incidence increases with age [10]. Across Europe, prevalence tends to be higher in Norway and Sweden compared to southern and eastern Europe [5-7, 11]. There are wide variations even globally, where people in Japan historically have had a gallstone prevalence of 3%, compared to a prevalence of 49% in the Pima natives of North America [12-14]. Gallstones are almost absent on the African continent and in children and young adults, even if prevalence tends to increase with increasing obesity globally and in younger ages [15].

1.2.4 Risk factors

In all age groups, women have a higher prevalence of gallstones than men. The difference between females and males is less pronounced in countries where pigment stones are more common, as in Asia [15]. One possible explanation for the sex discrepancy is female sex hormones and alternations in hormonal levels [16]. Pregnancy is a known risk factor for gallstone formation. At least 10% of pregnant women are liable to develop biliary sludge or stones during their pregnancy, which disappear spontaneously after delivery in two-thirds of cases [17]. Increasing age, ethnic background and genetic susceptibility are other unchanging risk factors [15]. A Swedish study of 43,141 pairs of twins showed that the genetic effect accounted for 25% of cases with no differences in heritability between the sexes [18]. Other risk factors that can be altered and prevented are obesity, metabolic syndrome, rapid weight loss (bariatric surgery and low carbohydrate diets), certain diseases (cirrhosis, chronic haemolysis and Mb Crohn), certain medications (ceftriaxone, statins, oestrogen therapy and oral contraceptives), total parenteral nutrition and prolonged fasting [7, 15, 19-23]. A diet rich in simple sugars and saturated fat is associated with a high risk of gallstone formation. Fibres, unsaturated fats, and a moderate consumption of alcohol tend to reduce the risk for gallstone formation [24-26].

1.2.5 Symptoms

Most patients with gallstones (70%-80%) are asymptomatic, and gallstones are a common incidental finding on CT scans, MRI and abdominal ultrasonography [10, 27]. The average risk of developing gallstone-related pain or complications is low, 1%-3% per year [28]. The typical patient with gallstone-related pain (biliary colic) complains of upper abdominal pain, often with radiation to the back or right shoulder. The pain is severe and starts abruptly with increasing intensity. Associated nausea and vomiting are common. Symptoms may arise after food intake, usually 30 minutes to 1 hour after a meal, but it may also be unrelated to eating. The symptoms usually resolve gradually over 1-5 hours [27]. If they last longer, a complication should be suspected. Biliary colic is usually caused by a temporary obstruction of the gallbladder outflow. This results in a distension of the gallbladder or biliary tract, which activates visceral sensory neurons and causes pain [27]. Laboratory blood tests are usually normal in uncomplicated biliary colic. Although gallstones are often asymptomatic, they may cause more serious complications. Stones in

the deeper bile ducts may cause bile obstruction or pain. These stones can also provoke acute pancreatitis or cholangitis. Rarer complications include gallstone ileus, (when stones from the gallstone erode through the gallbladder wall and obstruct the intestine) and Mirizzi's syndrome (compression of the hepatic bile ducts by proximal gallbladder stones in chronic inflammation). The most common gallstone-related complication is acute calculus cholecystitis, the main focal point of this thesis.

1.3 ACUTE CHOLECYSTITIS – GALLBLADDER INFLAMMATION

The term cholecystitis refers to an inflammation of the gallbladder wall. In 90%-95% of cases, it is a gallstone complication. However, 5%-10% of cases have a gallbladder inflammation without gallstones, an acalculous cholecystitis [29]. It usually occurs in critically ill and often immunosuppressed patients, as a consequence of gallbladder ischaemia and/or stasis [29]. Both acute and chronic cholecystitis are present in the clinical setting. Acute cholecystitis is an acute inflammation, resulting in oedema, lymphocyte invasion and hyper-vascularisation of the gallbladder wall. Chronic cholecystitis is a consequence of repeated attacks of gallbladder outlet obstruction, episodes of acute cholecystitis, and mechanical irritation. It results in a thickening of the gallbladder wall due to fibrosis. The thickening is asymptomatic, and chronic cholecystitis is a histopathological diagnosis, often visualized by radiology or during surgery. The fibrosis dissolves the otherwise evident mucosal and submucosal layers, and often affects adjacent structures, which may complicate surgery. Although there is no evidence that chronic cholecystitis increases morbidity, it may be important to identify the condition preoperatively when assessing the operative risk [30]. Assessing potential difficulties beforehand is important in improving surgical safety. Patients with chronic cholecystitis may benefit from a surgeon with extensive experience in gallstone surgery [31]. A thickening of the gallbladder wall with calcifications is called a porcelain gallbladder. This condition has been associated with a malignant potential, but this connection is still the subject of discussion [32].

1.3.1 Pathophysiology – gallbladder inflammation

Like biliary colic, acute cholecystitis seems to be associated with cystic duct obstruction, but, in this case, the obstruction initiates an inflammatory cascade of events [33]. The obstruction of the cystic duct results in a distention of the gallbladder and an increased secretion of fluids and prostaglandins, which causes inflammation [34-36]. The result is a tense, richly vascularised and oedematous gallbladder. The elevated pressure in the wall obstructs the blood flow, resulting in vascular thrombosis. The first oedematous stage can be followed by an increase of inflammation, resulting in areas of haemorrhage and necrosis [37].

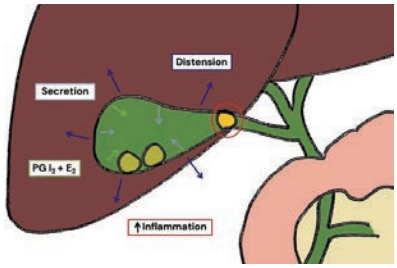
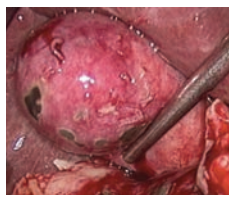


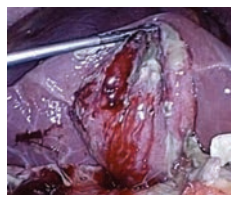
Figure 1.3.1a Pathophysiology

In most cases, the inflammation is initially sterile, but a secondary infection may occur. Bacterial invasion can result in further necrosis and gangrene of the gallbladder wall, as well as gas in the lumen (emphysematous cholecystitis) [38]. For some reason, the more complicated operations tend to accumulate on Friday afternoons. In Swedish, there is the somewhat ironic expression, "Fredagsgalla" (i.e., Friday cholecystectomy).

Mild cholecystitis



Gangrenous cholecystitis



Emphysematous cholecystitis

Figure 1.3.1b Different grades of cholecystitis

1.3.2 Epidemiology

Incidence of acute cholecystitis is nearly equal in men and women, unlike gallstones in general [10, 39]. The annual risk of gallstone-related symptoms when gallstones are present is 1%-3% [28]. Twenty percent of symptomatic patients suffer at least one episode of acute cholecystitis [23] and 10%-15% get cholecystitis without a prior pain episode [28, 40].

1.3.3 Symptoms

Acute cholecystitis often begins with biliary colic, gradually developing into constant pain. Fever, nausea and vomiting are common but not always present [41]. Murphy's sign - palpating the gallbladder under a deep breath, thereby provoking a sudden stop in the inspiration - is often positive [41]. The level of C-reactive protein (CRP) may be elevated, and a high white blood cell (WBC) count indicates a more severe inflammation [37, 42]. In more severe cases with sepsis, patients may suffer from multiorgan failure, usually if a secondary infection or complications such as perforation, pericholecystic abscess, biliary fistula or bile peritonitis have occurred [37]. However, symptoms might be more diffuse, especially in patients with excess abdominal tissue since the omentum may cover the gallbladder and isolate it from the pain-sensitive peritoneum. Consequently, diffuse abdominal pain and slightly elevated WBC may be the only indications of a severely inflamed gallbladder. This is more common in individuals with a lot of internal adipose tissue and this tendency is sometimes called "Gubbgalla" in Swedish (i.e., "old man's gallbladder).

1.3.4 Tokyo Guidelines

Early in the 21st century, a panel of experts undertook a systematic review of articles about the treatment and diagnosis of acute cholecystitis. During an international consensus meeting in Tokyo, they agreed on new diagnostic criteria and a severity grading, called the "Tokyo Guidelines 2007" [37, 43, 44]. The guidelines were revised in 2013 (TG13) and 2018 (TG18) and are now widely adopted and used in clinical practice, as well as in research. The diagnostic criteria in the Tokyo Guidelines 2007 have high sensitivity and specificity [43, 44]. Other clinical criteria for acute cholecystitis exist. Two examples are the American Association for the Surgery of Trauma (AAST) grading scale for emergency surgery and the Parkland criteria for intraoperative severity grading [45–47]. In this thesis, the Tokyo guidelines (TG18) will be used for diagnosis and severity grading in PAPER V.

DIAGNOSTIC CRITERIA, TG18

TOKYO GUIDELINES – DIAGNOSTIC CRITERIA FOR ACUTE CHOLECYSTITIS	
A	Local signs of inflammation ▪ Murphy's sign ▪ Pain/mass/tenderness in the right upper quadrant
B	Systemic signs of inflammation ▪ Fever, elevated CRP, elevated white blood cell (WBC) count
C	Imaging findings characteristic of acute cholecystitis ▪ Abdominal ultrasound, CT, or MRI

Suspected diagnosis: One item in A + one item in B
Definite diagnosis: One item in A+ one item in B + C

SEVERITY GRADING, TG18

TOKYO GUIDELINES – SEVERITY GRADING FOR ACUTE CHOLECYSTITIS	
Mild (Grade I)	Acute cholecystitis in a healthy patient with mild inflammatory changes in the gallbladder, making cholecystectomy a safe procedure.
Moderate (Grade II)	Any of the following conditions: ▪ WBC >18 ▪ Palpable tender mass in the upper right quadrant of the abdomen ▪ Duration of symptoms >72 hours ▪ Marked local inflammation (gangrenous cholecystitis, hepatic or pericholecystic abscess, biliary peritonitis, emphysematous cholecystitis)
Severe (Grade III)	Signs of any of the following organ/organ system dysfunctions: ▪ Cardiovascular dysfunction: hypotension requiring dopamine or noradrenalin infusion ▪ Neurological dysfunction: decreased level of consciousness ▪ Respiratory dysfunction: PaO_2/FiO_2 ratio <300 ▪ Renal dysfunction: oliguria, creatinine >2.0 mg/dl ▪ Hepatic dysfunction: PK–INR >1.5 ▪ Haematological dysfunction: platelet count <100

1.4 TREATMENT OF CHOLELITHIASIS AND ACUTE CHOLECYSTITIS

1.4.1 Overview

The standard treatment of recurrent biliary colic and acute cholecystitis is surgical removal of the gallbladder. I will briefly mention other treatment options for cholelithiasis and acute cholecystitis, but this thesis will focus mainly on the definitive surgical treatment.

1.4.2 Anatomy

Due to variations in embryological development, the anatomy of the gallbladder, cystic duct and cystic artery may differ considerably [48]. The biliary tree is said to be the organ system that varies the most and "the most consistent feature of biliary anatomy is its inconsistency" [49]. Varying anatomy, and possible accessory and aberrant ducts, are surgical challenges that increase the risk for injury to both vessels and bile ducts during surgery [49, 50]. An overview of the anatomy one can expect to encounter is shown below. However, both the arterial supply and the biliary tree vary considerably, and it is wise to expect the unexpected. The most common anatomical variations can be found in previous publications [51, 52].

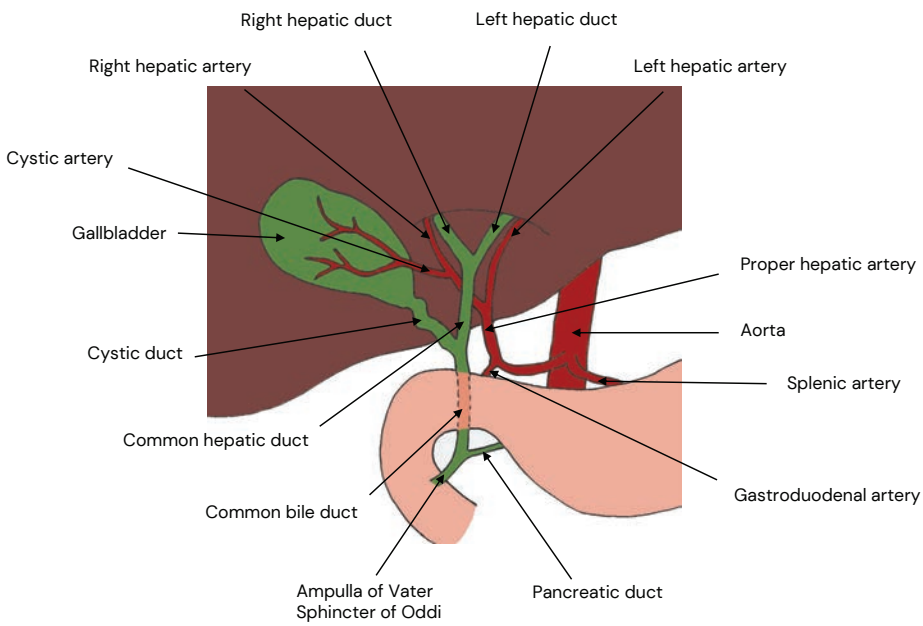


Figure 1.4.2 Basic anatomy

1.4.3 Treatment of cholelithiasis – biliary colic

The treatment of biliary colic is focused on pain control, usually achieved by the administration of non-steroidal anti-inflammatory drugs (NSAIDs) or opioids [10, 53]. If the pain disappears, an elective ultrasonography of the liver and gallbladder is a common routine, usually within four weeks. If the pain persists despite adequate medical therapy, an acute ultrasound or CT scan is performed to differentiate from other diagnoses, in particular acute cholecystitis [10, 27]. Both asymptomatic and symptomatic patients have a benign natural history. The expression "one attack is no attack" is common, and the literature confirms that asymptomatic patients and patients with only a few pain episodes can be treated in a conservative way, with the expectation and hope of recovery [27, 28, 54, 55]. However, patients should be given information about the recurrence rate of 50% during the first year, and the risk of complications secondary to gallstones [27, 56]. The recommended treatment for patients with recurrent biliary colic is surgical removal of the gallbladder, cholecystectomy [10, 27, 56]. An ongoing British multicentre, randomized trial (C-Gall) will hopefully give us a better understanding of the benefits of the different available approaches [57]. A prophylactic cholecystectomy in asymptomatic patients may be considered in patients with big gallbladder polyps and porcelain gallbladder [58]. It can also be considered in patients at high risk of becoming symptomatic, such as children and patients scheduled for obesity surgery, but the evidence is scarce and there are currently no clear guidelines regarding prophylactic cholecystectomy in these groups [59, 60].

1.4.4 Alternative treatments for biliary colic

Extracorporeal shock wave lithotripsy (ESWL) and medical treatment with ursodeoxycholic acid may be alternatives in non-operable patients and those who decline surgery, but the recurrence rate is high [61–63]. In some countries, ursodeoxycholic acid is used to prevent gallstone formation in patients with an expectedly high weight loss, as after bariatric surgery [23, 64]. None of these options is in clinical use in Sweden today. Gallstones in the deeper bile ducts are present in approximately 9% of elective operations and 20% of acute operations [65]. Common bile duct stones (CBDS) should also be removed, and the recommendations include all stones, without size limit [10, 66, 67]. In Sweden, stone removal is usually done with intraoperative or postoperative endoscopic retrograde cholangiopancreatography (ERCP), transcystic stone extraction or more rarely open or laparoscopic choledochotomy. Alternative managements are flushing small stones to the intestine or leaving them for spontaneous passage (not recommended) [39]. If the patient still has a gallbladder, the recommendation is to perform a cholecystectomy with intraoperative CBDS removal [10]. The available options and strategies for treating CBDS will not be discussed further in this thesis.

1.4.5 Treatment of acute cholecystitis

There is national and international consensus that the treatment of choice for most patients with acute cholecystitis is surgical removal of the gallbladder [44, 56, 68-72]. Conservative treatment with expectancy, with or without antibiotics, results in a high rate of readmission during the first five years after the first acute episode [73]. Gallstone-related complications often occur within six weeks of discharge for conservatively treated acute cholecystitis [74]. The readmission rate tends to be higher in younger patients [75]. Gallbladder drainage, cholecystostomy, might be an option in critically ill patients when cholecystectomy cannot be performed safely. However, cholecystostomy has been shown to result in higher post-procedural morbidity and mortality and longer hospital stays compared to cholecystectomy [76-79].

1.5 SURGICAL TREATMENT

Surgical removal of the gallbladder by cholecystectomy can be performed through open surgery (laparotomy), conventional laparoscopy or robotic-assisted laparoscopy. Since the first laparoscopic cholecystectomy in the late 1980s, this has become the gold standard worldwide [80-84]. Robot-assisted cholecystectomies are not yet routinely used. In 2022, some 14,984 cholecystectomies were performed in Sweden [39]. Of these, 6,908 (46%) were acute (including acute cholecystitis, acute pancreatitis and patients with biliary colic undergoing surgery in an acute setting) and 8,076 (54%) were elective/planned operations. One fifth (22%) of all cholecystectomies were performed due to an acute cholecystitis. Only 709 (4.7%) of procedures were completed with the open technique [39]. The operating time and hospital stay depends on the anatomical conditions and severity grade of a potential inflammation [44]. A cholecystectomy can take anywhere from less than an hour to more than four hours. Most patients with biliary colic can undergo surgery in day-care surgery [85]. Patients with mild cholecystitis can often be discharged within one to two days after surgery, but significantly longer stays are not uncommon in cases of severe inflammations, open surgery and if there is a complication.

1.5.1 Laparoscopic cholecystectomy

The standard laparoscopic operation, as performed in Sweden, starts by preparing the patient for surgery. After anaesthesia, sterilization and draping, the operation begins by administration of local anaesthetics in the intended skin incisions. The lead surgeon, an assistant and the surgical nurse are positioned around the patient. The main procedural steps are:

1. Abdominal access

An abdominal open access below the umbilicus is commonly used. A 10 - 12 mm laparoscopic port is inserted, and pneumoperitoneum is created with CO_2. An alternative is to use a Verres needle in Palmer's point, thereby creating the pneumoperitoneum before port insertion. A 30-degree laparoscope is inserted through an optical trocar. The gallbladder is identified, and the abdominal cavity is inspected to identify adherences or other complicating factors. A second 10 - 12 mm epigastric and two 5 mm ports are

inserted in the right flank. Four laparoscopic ports are usually used in Sweden. In case of difficulty additional ports can be added for better access.

2. Dissection

The gallbladder is retracted in a cranial direction with a grasper to aid in visualising the cystic duct. This traction is maintained by the assisting surgeon. The dissection and mobilisation of the gallbladder are performed with a surgical energy device. Adherences due to an ongoing or previous inflammation are divided. The dissection usually starts where the cystic duct is estimated to enter the gallbladder, or preferably a little above this region. The sulcus of the caudate process (Rouviere's sulcus) is an important landmark to identify. It is a 2-5 cm long liver fissure between the right lobe and caudate process, including the right hepatic artery, portal vein and hepatic bile duct [86]. The dissection should not go below it to avoid an injury to the deeper bile ducts. An alternative is to start from the top of the gallbladder, the fundus-first approach. The purpose of the dissection is to free the cystic duct and artery from surrounding tissues.

3. Intraoperative cholangiography

In Sweden, intraoperative cholangiography is routinely performed to visualise the anatomy of the biliary tree. This is somewhat unusual in the international perspective. In most other countries, cholangiography is done selectively in cases of uncertainties regarding anatomy or suspicion of common bile duct stones. When the anatomy is clear and the cystic duct and artery are identified, a proximal clip is applied on the cystic duct, the duct is cut open, and a small catheter is inserted. Contrast is injected and X-rays are used to visualise the biliary tree. An incomplete depiction of the tree is a warning sign, indicating either an obstruction, a misplaced catheter or contraction of the bile ducts. Alternatives to a conventional X-ray are laparoscopic and endoscopic ultrasound and fluorescence cholangiography [87]. Intraoperative removal of CBDS is recommended. When the anatomy is visualized and no stones remain, the cystic duct can be divided. This is usually done in between clips, usually with two clips at the proximal end. The cystic artery is likewise divided between clips or with the energy instrument.

4. Gallbladder removal and wound closure

The gallbladder is dissected from the liver and extracted in a retrieval bag through the sub-umbilical incision. The liver is inspected, and should there be any oozing bleeding, it is stopped with the energy instrument or by adding a haemostatic product. Remaining bile and blood are aspirated, the ports are extracted, and the fascia and skin are closed with absorbable sutures. A standard, or more complicated, laparoscopic cholecystectomy can be seen at: *https://vardgivare.regionorebrolan.se/sv/vardriktlinjer-och-kunskapsstod/videoarkivet-uso/Laparoskopisk-kirurgi/Gallkirurgi/* [88].

Figure 1.5.1a Placement of laparoscopic ports

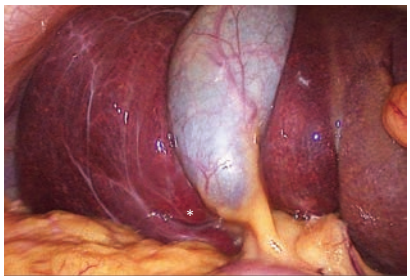


Figure 1.5.1b Abdominal access

1. Inspection of the abdominal cavity.
2. Placement of a grasper on the top/fundus of the gallbladder.
3. Identify Rouviere's sulcus *.

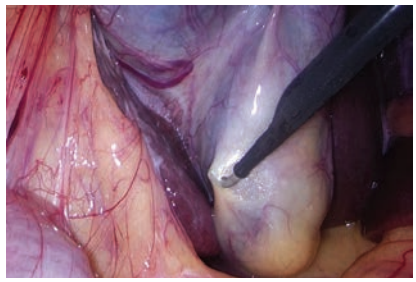


Figure 1.5.1c Dissection

1. Dissection of the cystict duct and cystic artery with an energy device.

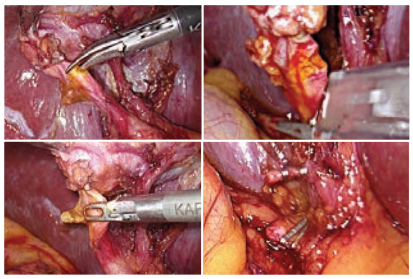


Figure 1.5.1d Intraoperative cholangiography

1. Opening of the cystic duct.
2. Insertion of a catheter.
3. Proximal duct closure with two clips.
4. Division of the duct.

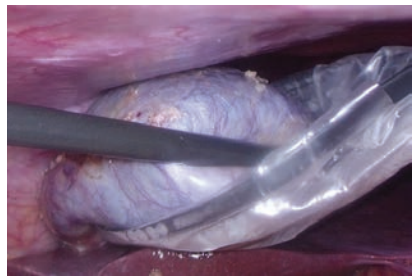


Figure 1.5.1e Gallbladder removal and wound closure

1. The gallbladder is dissected from the liver and placed in a retrieval bag.
2. The retrieval bag is extracted through the umbilical incision.
3. Remaining bile and blood are aspirated.
4. Ports are removed and the wounds are sutured.

1.5.2 Open cholecystectomy

The open technique has traditionally been performed with a 10 - 15 cm right subcostal incision, often followed by fundus-first dissection of the gallbladder and then manual dissection in Calot's triangle. When only the cystic duct and artery remain attached to the gallbladder, they are divided, and the gallbladder removed. Since the introduction of the laparoscopic operation, the open approach has gradually been abandoned. It is seldom used as a first-line approach but may be necessary in more complicated cases. Inflammation with difficult anatomy is the most common reason for conversion from laparoscopic to open surgery [89]. Increasing age, male sex and a high WBC count have been identified as predictors of conversion [90]. The open approach inflicts greater surgical trauma with a higher level of systemic immune response compared to laparoscopic surgery [91]. Younger surgeons today have limited experience with the open approach. Nevertheless, surgeons are expected to handle it in complicated situations, which is an educational challenge.

1.5.3 Robot-assisted cholecystectomy

Robotic surgery is a well-established alternative to laparoscopic surgery for many complex surgical procedures, but the advantage in less complex procedures such as cholecystectomies is under debate. The use of robot-assisted cholecystectomy is increasing globally, especially in the USA [92]. A recently published cohort study demonstrated higher rates of bile duct injuries for robot-assisted cholecystectomy, compared to laparoscopic cholecystectomy [93]. Robot-assisted cholecystectomy is still rare in Sweden. In 2023 there are few surgeons who see an advantage to robotic surgery in cholecystectomy, due to limited recourses, increasing costs and the accessible and relatively easy laparoscopic approach. However, as costs decrease and access to robots improves, it is possible that this will change. The future development of robotic surgery in cholecystectomy is difficult to predict.

1.5.4 Additional considerations in surgical treatment

Antibiotic prophylaxis is not required in uncomplicated elective cholecystectomies [10, 70, 94]. The evidence is somewhat more divergent for acute cholecystitis but patients with a mild to moderate cholecystitis should not have antibiotics recommended since the inflammation is often sterile [10, 94]. A recent RCT demonstrated a lower rate of surgical-site infections with antibiotic treatment, but no difference in other complications [95]. However, antibiotics may be beneficial in severe cases to prevent gallbladder perforation and intra-abdominal and hepatic abscesses [10, 96, 97]. The contaminating bacteria are often escherichia coli, anaerobes, or from the enterobacteriaceae family [98, 99]. The risk for a thromboembolic event is low in laparoscopic cholecystectomy. An increased risk for bleeding has been associated with preoperative administration of anti-thrombotic drugs [100]. Most guidelines recommend prophylactic treatment only to high-risk patients and in cases of long operating times [101, 102].

1.5.5 The Swedish National Quality Registry of Gallstone Surgery

Nearly all cholecystectomies and ERCP procedures performed in Sweden are registered in the Swedish Registry for Gallstone Surgery and Endoscopic Retrograde Cholangiopancreatography, called GallRiks [103]. The registry includes information about patient characteristics, surgery-related parameters, intraoperative complications and a 30-day follow-up to register length of hospital stay (LOS) and postoperative complications. The registry publishes an annual report, including statistics on cholecystectomies and ERCP procedures registered the preceding year. The results are presented both on a national and centre level. GallRiks has a central role in all the papers included in this thesis and will be explained and discussed further.

Figure 1.5.5 GallRiks logotype

1.6 SURGICAL COMPLICATIONS

Complications after surgery are often divided into intraoperative, postoperative, and overall /total complications. Intraoperative complications occur during surgery and are often procedure related. Some examples in cholecystectomy are bleeding, intestinal perforation, injury to other visceral organs and bile duct injury. In 2022, an intraoperative complication occurred in 1.2% of the elective and 1.9% of the acute procedures [39]. One of the most feared surgery-related complications is a bile duct injury. The incidence of bile duct injury has been stable at around 0.3%, and 1.5% when including postoperative bile leakage [10, 104-106]. Patients with acute cholecystitis have twice the risk for a biliary injury compared to patients without acute cholecystitis. The risk is correlated with the Tokyo severity grade [107]. Postoperative complications include all complications occurring during the first 30 days. The rate of postoperative complications was 544 (6.7%) in elective surgery and 783 (11.3%) in acute surgery in 2022. Thirty-day mortality in Sweden is around 0.05% in elective and 0.33% in acute cholecystectomy [108]. Complications are more common in male patients than female patients. In 2022, nearly 30% of the open cholecystectomies in GallRiks were registered with a complication [39]. In addition, studies show a significantly longer hospital stay and recovery time after open surgery and the rate of postoperative infections and pneumonia tend to be higher, with longer sick leaves [109-113].

REGISTERED COMPLICATIONS IN THE 2022 ANNUAL GALLRIKS REPORT							
N (%)	**Male**	**Female**	**Elective**	**Acute**	**Laparoscopic**	**Open**	**Total**
Number of patients	5,427 (36.2)	9,557 (63.8)	8,076 (53.9)	6,908 (46.1)	14,275 (95.3)	709 (4.7)	14,984
Intraoperative complications	111 (2.0)	118 (1.2)	99 (1.2)	130 (1.9)	165 (1.2)	64 (9.0)	229 (1.5)
Postoperative complications	576 (10.6)	751 (7.9)	544 (6.7)	783 (11.3)	1,132 (7.9)	195 (27.5)	1,327 (8.9)
Hospital stay >3 days	653 (12.0)	714 (7.5)	217 (2.7)	1,150 (16.6)	951 (6.7)	416 (58.7)	1,327 (9.1)

1.6.1 Severity grading of complications

Surgery-related complications include a broad spectrum of diseases and conditions of varying severity. Some examples are urinary retention, superficial wound infections, myocardial infarction, thrombosis, and death. The need for international consensus on severity grading of complications was the rationale behind the Clavien-Dindo classification, which is well-established today [114]. The Clavien-Dindo classification has been registered for all complications in GallRiks since 2020.

CLAVIEN-DINDO GRADING OF SURGICAL COMPLICATIONS USED IN GALLRIKS		
Grades	**Definitions of Grades**	**Explanation**
CD1	Any deviation from the normal course	Any deviation from the normal course, without need for interventions, which has been controlled with normal medications, simple infusions, and physiotherapy. Includes incision of superficial infections and abscesses.
CD2	Medical treatment	A complication requiring medical treatment outside the normal spectrum included in CD 1, including blood transfusion, antibiotics, and total parenteral nutrition.
CD3a	Intervention without anaesthesia	A complication needing surgical, radiological, or endoscopic intervention. Not requiring general anaesthesia.
CD3b	Intervention with anaesthesia	A complication needing surgical, radiological, or endoscopic intervention. Requiring general anaesthesia.
CD4a ICU	Organ failure	Single organ failure, including dialysis. Intensive care unit (ICU) care.
CD4b ICU	Multi-organ failure	Multi-organ failure. ICU care.
CD5	Death	Death of the patient.

1.6.2 Postoperative patient satisfaction

The treatment for both cholelithiasis and acute cholecystitis aims at eliminating symptoms and improving health-related quality of life (QoL), with a low complication rate. However, persistent abdominal pain 6 to 12 months after elective surgery has been demonstrated in up to 30%-40% of patients [115, 116]. Different explanations for postoperative pain have been identified: surgery-related complications, persisting or recurrent gallstones, physiological changes due to an altered bile acid metabolism, psychological factors, and the most important factor -- previously undiagnosed functional gut disease such as dyspepsia or irritable bowel syndrome [117]. Biliary colic has been shown to be resolved in 94.8% of patients who undergo cholecystectomy, but new symptoms such as bowel urgency (8.5%), diarrhoea (8.4%) and frequent bowel movements (9.6%) have been reported [116]. A large Dutch randomized study studied a restrictive strategy for cholecystectomy [115]. Their five criteria for cholecystectomy were: (1) severe pain attacks, (2) epigastric or right upper quadrant pain, (3) radiating back pain, (4) pain duration of 15-30 minutes or longer, and (5) pain relief with analgesic. Despite this, only 54% of patients were pain free after 12 months, compared to 60% in usual care. However, fewer patients underwent surgery with the restrictive strategy [115]. Female patients who underwent surgery on the indication of biliary colic have demonstrated higher levels of postoperative pain and lower postoperative health scores [118]. Preoperative pain at least once per month, as well as the patient's own conviction that the pain is caused by gallstones, are important factors in predicting postoperative outcome [119]. The high percentage of postoperative pain

and functional disorders stresses the importance of careful patient selection and providing thorough preoperative information.

1.6.3 Patient-reported outcome measures

Different instruments have been suggested for measuring the patients' quality of life (QoL) after surgery. These are commonly called patient-reported outcome measures (PROMs). Different PROMs are used in laparoscopic cholecystectomy. In a recently published review, seven different instruments were in clinical use [120]. Most of these compare scores before and after surgery, but some are used only after surgery. GallRiks includes a voluntary health survey, entitled SF-36 ® [121]. It was introduced as a pilot project in 2006 and is distributed before and 6-9 months after surgery. Nine Swedish hospitals used the questionnaire in 2022 [39]. SF-36 includes 36 items (SF=short form) with multiple choice answers and takes 15-20 minutes to complete. The survey can provide important information related to the patients' postoperative satisfaction. The importance of the patient's own convictions mentioned in the previous section has been demonstrated in a GallRiks-based study using SF-36 [119]. Another well-established simple PROM is the EQ-5D, and its updated versions EQ-5D-5L and EQ-5D-5Y (children/youth version) [122, 123]. The updated version includes five questions, representing five different dimensions. Each question has five levels ranging from no problem to extreme problems. In addition, there is an EQ VAS scale where the patient grades their self-rated health on a scale from "the best health you can imagine" (100) to the "worst health you can imagine" (0). It takes only a few minutes to complete the survey. EG-5D-5L will be used in PAPER V, the randomized controlled trial in this thesis. Researchers are currently working on a new PROM for patients undergoing cholecystectomy, which will hopefully be integrated into GallRiks.

1.7 SURGICAL SAFETY IN GALLSTONE SURGERY – OVERVIEW

Surgical care is an important part of health care worldwide. The intention with surgery is to save lives. However, unsafe surgery is related to patient suffering, disabilities and mortality (the crude mortality rate after major surgery is 0.5% - 5% [124]). According to the World Health Organization, at least half of the cases in which surgery leads to harm can be prevented [125]. In addition, almost half of all adverse events in hospitalized patients in industrialized countries are related to surgical care.

The treatment for symptomatic cholelithiasis and acute cholecystitis is the surgical removal of the gallbladder. Thus, surgical safety is a cornerstone in improving outcomes for these patients. The expression *surgical safety* is complex and has different aspects. Organisational structures and adequate resources are essential and checklists like the WHO Surgical Safety Checklist are used in many countries [125]. Surgical safety can also be improved by competent health care workers, teamwork, and surgeons using standardized and established surgical techniques. This requires a safe and structured education for the coming generation of surgeons. Surgical safety is patient safety. The aim is to decrease suffering for the patients and to avoid preventable adverse events. Individual assessment and optimization of patients prior to surgery and a structured rehabilitation post-surgery are crucial. Aspects of surgical safety in gallstone surgery on organizational, individual, and technical levels are the focal point of this thesis. The areas will be illustrated with these icons:

ORGANIZATION

INDIVIDUAL

TECHNIQUE

1.8 IMPROVING SURGICAL SAFETY ON THE ORGANIZATIONAL LEVEL

Surgical safety on the organizational level is a complex issue. Here, I will focus on factors that are important in understanding the rationale behind the papers in this thesis: the timing of surgery for acute cholecystitis, the importance of surgical volumes and a bonus, the surgical black-box concept that video recordings offer.

1.8.1 Timing of surgery in acute cholecystitis

Most surgeons agree that patients with acute cholecystitis should undergo cholecystectomy, but the optimal timing is still disputed. Traditionally, two approaches have been adopted: either surgery during the first hospital admission or delayed elective surgery after two or three months. The Tokyo Guidelines (TG18) recommend acute cholecystectomy during the first hospital admission in patients with mild and moderate acute cholecystitis [126]. Patients with severe cholecystitis also benefit from early surgery, but careful optimization for surgery and surgical expertise are required. The suboptimal alternative in severely ill patients is conservative treatment and a delayed elective operation when the patient is stable [126]. During the wait for elective surgery, inflammation may flare up again. Recurrent inflammations increase the risk for fibrosis, and delayed surgery may therefore be more complicated. Since mortality and bile duct injuries are rare, it is difficult to get statistical power but most studies recommend early surgery for acute cholecystitis [127]. A decreased incidence of wound infections and a shorter hospital stay have also been demonstrated [109, 128]. A risk reduction in bile duct injuries has been noticed in some studies, even if the total complication rate seems to be the same [129]. Postponing treatment and planning for an elective operation involves waiting. Apart from the risk of recurrence, this may affect quality of life, with impacts on physical health, on social and psychological life, and on costs to society [74, 129, 130]. Cost efficiency is one main reason why surgery should be performed early [75, 131-133]. However, patients with acute cholecystitis are still treated conservatively with a delayed elective procedure, mainly due to lack of resources. In 2023, the Swedish National Guidelines for Gallstone-Related Diseases were published, further emphasising the importance of acute surgery in cholecystitis, during the first hospital stay [10]. The evidence is in line with previously published RCTs and other international guidelines [10, 44, 56, 68-72, 134].

1.8.2 The definition of early surgery

The Tokyo Guidelines of 2007 recommended an operation for acute cholecystitis as soon as possible after hospital admission [135]. In the revised guidelines from TG13, the recommended time span was defined as within 72 hours of admission [136]. In the latest guidelines from 2018, this was further elaborated. Specifying the onset of symptoms can be difficult and symptoms may vary widely. Sticking stubbornly to the time limit of 72 hours excludes many patients who are, in fact, operable. Varying criteria of early surgery exist in the literature: 24 hours after the onset of symptoms, 24 hours after hospital admission, 72 hours, 4 days and 1 week. When the guidelines were revised, two groups were identified based on the time from the onset of symptoms: within 72 hours and within 1 week (including the 72 hours). A meta-analysis showed no difference between early and late surgery regarding overall low rate of mortality, conversion, and complication [89]. Early surgery seems to reduce cost, overall hospital stays and the risk for readmission [126, 137, 138].

The conclusion in the 2018 Tokyo Guidelines is as follows: "If a patient is deemed capable of withstanding surgery for acute cholecystitis, we propose early surgery regardless of exactly how much time has passed since onset" [126].

1.8.3 Importance of surgical volumes

The importance of high hospital volumes for surgical safety in more complex procedures, such as cancer surgery, has been demonstrated previously [139-143]. This has been used as an argument for centralization of malignant and rare conditions to highly specialized centres [144]. As for gallstone surgery, the available evidence is more divergent. Some studies demonstrate lower costs, fewer conversions to open surgery and a decreased mortality rate, in high volume centres [145, 146 147]. Others show no difference in postoperative complications or conversions rates [148]. The importance of high individual volumes of cholecystectomies are also divergent. In some studies patients operated on by high-volume surgeons had shorter hospital stays and fewer readmissions, but no significant difference in major complications [149, 150]. However, other studies found an association between high-volume surgeons and fewer complications in high-risk patients and acute cholecystitis [151, 152]. If high-volume hospitals and high-volume surgeons have more favourable outcomes in cholecystectomy, it is important to assure high volumes to increase surgical safety on both the organizational and individual level.

1.8.4 Surgical safety and video recording

Video recording of laparoscopic procedures is important in increasing surgical safety by recording errors and adverse events, and to decrease distractions [153, 154]. Operative notes can be misleading and video recordings in addition to written medical records better represent what really happened in the operating room [155]. Most laparoscopic systems today can record and store films, usually for three months. Video-recordings are often referred to as the "black-box" concept in surgery, since they offer a way to go back in time and check what happened in case of complications [156]. Audio video recordings are even more informative and reduce irrelevant conversations [153]. Videos are also a valuable tool in surgical educational since residents and supervisors can look at procedures in retrospect and discuss the techniques. Recordings of rare procedures and complications can be viewed and shared by many surgeons. The Swedish collection of surgical videos, "Örebroarkivet" [88], offers a large collection of videos of common and less common procedures . The archive includes many recordings of laparoscopic cholecystectomies. It is possible to watch standard procedures but also recordings of rare anatomical variations and complications. The legal aspect of video recordings is, however, yet to be solved [10]. Audio video recording is routinely performed in all laparoscopic surgery at Mora hospital, and both the lead surgeon and the assisting surgeon operate with headsets.

1.9 SURGICAL SAFETY ON THE INDIVIDUAL LEVEL

Surgical safety on the individual level may include both patient- and surgeon-related factors. However, this thesis will mainly focus on the individual surgeon, with technical aspects discussed separately. Surgical education and gender equity in surgery will be discussed here -- Two important aspects of surgical safety on the individual level.

1.9.1 Surgical education in cholecystectomy

Gallstone surgery is a cornerstone of surgical education, and laparoscopic cholecystectomies are performed by most surgeons, at least during a period of their careers and during surgical training. Surgery is a practical specialty and continuous training, and clinical experience are needed to master a procedure. Guaranteeing surgical safety during the learning curve is of great importance. Training on laparoscopic simulators is a safe way of practicing surgical skills, before starting to operate on patients [157-159]. Many hospitals in Sweden have clinical training centres where it is possible to practice suturing and virtual laparoscopic training, via simulators. After and in parallel with simulator training, most surgical residents start to assist other surgeons in laparoscopic cholecystectomies. Thereafter, a gradual introduction to different procedural steps is natural. Placement of trocars followed by dissection of the gallbladder from the liver, cholangiography and eventually dissection in Calot's triangle are steps towards independence. In 2020, 55% of the centres performing laparoscopic cholecystectomies in Sweden had a compulsory "competence license" for residents, before performing cholecystectomies independently ("Gallkörkort" in Swedish) [160]. Despite the never-ending introduction of new techniques and instruments in surgery, studies on learning curves for different procedures are sparce and varying methodologies are used [161, 162]. This topic will be further discussed in PAPER IV in this thesis.

1.9.2 Gender equity in surgery – overview

One somewhat different aspect of surgical safety on the individual level is gender equity. In some countries, there is a general belief that male surgeons are better than female surgeons [163]. The surgical specialty is traditionally dominated by men. In general surgery, 32% of all Swedish surgeons were female in 2020, compared to more than 50% of all medical students and 48% of active physicians [164]. This is slightly higher than 27% in the UK, 22% in Japan and 22.6% in the USA [165-167]. Less is known about gender distribution in countries in South America and Africa. As an illustrative example, Rwanda had only two female surgeons in 2018 [163]. A summary of the history of female surgeons can be found in the appendix.

1.9.3 Gender equity in surgical safety

Gender-based research is a relatively new area of interest and most articles on the subject have been published in the past five to ten years. Studies on gender differences within the surgical specialty are sparce. A matched cohort study of 25 different common surgical procedures demonstrated similar complication rates but decreased 30-day mortality for female surgeons [168]. A Japanese study found no outcomes

difference between female and male surgeons in major general surgery (gastrectomies or low anterior resections), but female surgeons operated on more high-risk patients and had more open procedures [166]. A study from the USA demonstrated that female surgeons had fewer postoperative complications, shorter hospital stays and lower mortality rates, but the significance disappeared when matching surgeons working at the same hospital [169]. In general, female surgeons were younger and had less experience. To the best of my knowledge, there are no studies demonstrating worse outcomes for female surgeons, despite the general belief that male surgeons perform better. It is still unknown whether outcomes for female and male surgeons differ in cholecystectomy.

1.9.4 Explanations behind gender inequity in surgery

There are different explanations for inequities within the surgical specialty. Key issues include unfavourable work environments, a male-dominated culture, and social pressures [170]. Sexual harassment by male colleagues, seniors or patients is reported by up to 20% of surgical residents in the USA [170, 171] and by 55% of female surgeons in Ecuador [172]. In addition, 48% - 65% of female surgeons report gender discrimination [171, 172]. Many countries have developed processes and protections against gender discrimination on a systemic level, but it is still common with more subtle forms of interpersonal discriminations, often described as microaggressions [173, 174]. Many studies on gender differences are from North America or Europe. Throughout the world, the lack of female role models and mentorship seems to be a key factor behind why females choose other specialties or why so many female surgeons leave the specialty [163, 170, 175, 176].

1.10 IMPROVING SURGICAL SAFETY ON TECHNICAL LEVEL

Improving surgical techniques in cholecystectomy is important for increasing surgical safety. Most measures aim at decreasing the rate of surgical complications. Surgical technique based on important anatomical landmarks, the use of cholangiography and instrument handling will be discussed here.

1.10.1 Critical view of safety

When the laparoscopic technique was introduced, the previously mentioned advantages of decreased mortality, morbidity, and complication rates were noticed very quickly. Nevertheless, the rate of bile duct injuries increased. The trend shifted after the initial learning curve, but the bile duct injury rate remained higher than that of open surgery, even in high volume centres [177, 178]. One of the main reasons for serious bile duct injuries is misinterpretation of the anatomy. The common bile duct can be mistaken for the cystic duct. There are also aberrant ducts, which may be mistaken for the cystic duct [179, 180]. In 1995, Strasberg et al. did an analytical review and introduced the concept of the "critical view of safety" (CVS), a way of identifying the crucial structures [181]. According to their definition, the critical view of safety has three requirements:

1. The triangle of Calot must be cleared of fat and fibrous tissue. The common bile duct does not have to be exposed.
2. The lowest part (1/3) of the gallbladder is separated from the liver, and the liver bed behind the gallbladder, also known as the cystic plate, should be visualized.
3. Only two structures bridge to the gallbladder.

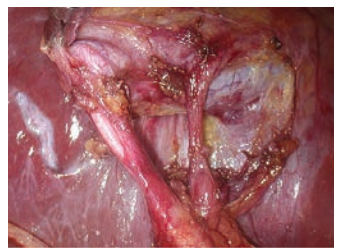


Figure 1.10.1. The Critical View of Safety

If these three criteria are fulfilled, a CVS is attained [180, 181]. The view should be clearly visible from both an anterior and posterior view. It is very important to strive for a CVS in laparoscopic cholecystectomy. If the CVS is unattainable, the importance of intraoperative cholangiography as a safety measure increases. Causing a severe bile duct injury cannot be considered as anything but a surgical disaster. Nevertheless, every surgeon with long experience of gallstone surgery is expected to manage complicated situations, and inevitably faces the risk of causing a bile duct injury. A critical view of safety is considered a crucial surgical step in the clinical studies in this thesis.

1.10.2 Cholangiography

An additional safety measure in cholecystectomy is to perform an intraoperative cholangiography. This is the standard routine in Sweden and, during 2022, cholangiographies were performed in 89.2% of the elective and 90.7% of the acute procedures [39]. A cholangiography shows common bile duct stones, atypical anatomy, obstructions, stenosis, and bile duct injuries.

The requirements for a normal cholangiogram are as follows [182].

1. Contrast in the common bile duct, hepatic duct and the left and right liver branches.
2. Assessment of the length of the cystic duct and its location in relation to the junction with the common bile duct.
3. Assessment of the diameter of the common bile duct (normally <6-7 mm).
4. No stenosis or suspected stones.
5. Contrast in the duodenum.

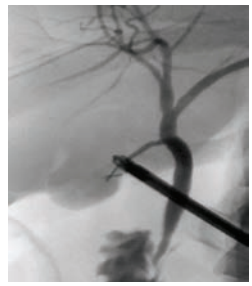


Figure 1.10.2 A normal cholangiogram

1.10.3 Energy instruments used for dissection

The most established technique used for gallbladder dissection is monopolar electrocautery. The instrument commonly used for this is shaped like a hook, which makes it possible to both lift and separate tissue, and to use the curved part of the instrument directly on the tissue. The hook is heated by an electric current, resulting in thermal spread. However, electrocautery dissection is known to cause rather extensive thermal spread with the risk of thermal injury to surrounding tissue. Bowel and bile duct injury may be inflicted by the instrument, especially during the learning curve [179].

An alternative approach is ultrasonic dissection. Ultrasonic energy dissection was developed in the late 1980s and has become more widespread and popular in the past 15 years [183, 184]. The compression of tissue and vessels is essential, and the instrument is formed like scissors with an active and a passive blade. The instrument uses electrical energy from a generator, which is converted into mechanical motion and vibration of the instrument's active blade [184]. Frictional heat generation breaks hydrogen bonds and coagulates proteins. Cutting and coagulation take place simultaneously and at a lower temperature than with the hook, with minimal lateral thermal spread. This closes blood vessels up to seven millimetres in diameter and lymphatic vessels more precisely. The instrument is frequently used in bariatric surgery and various other procedures. The blades on the first versions were blunt, which may be a disadvantage in the dissection of Calot's triangle. Later versions are more pointed and slightly curved.

Electric current
↓
Heating of instrument
↓
Thermal spread
↓
Denaturation of proteins and coagulation in surrounding tissue (60°C)
↓
Drying of tissue (100°C)
↓
Carbonization (150°C)

Compression of tissue
↓
Electric current converts into mechanical motion
↓
Vibration of active blade (55 500 Hz)
↓
Frictional heat generation
↓
Denaturation and coagulation in an area of +/- 1mm (60°C)
↓
Drying of tissue (100°C)

Figure 1.10.3 Simplified comparison of electrocautery and ultrasonic dissection (Harmonic® HD1000i)

In laparoscopic cholecystectomy, the use of the ultrasonic dissector may be justified by its faster dissection, better vessel sealing capacity and less thermal tissue injury compared to electrocautery [185, 186]. Energy dispersion is said to be less than in electrocautery dissection, but the instrument, especially the active blade, gets hot and can cause thermal injury to nearby structures [187]. Ultrasonic dissection in elective laparoscopic cholecystectomies has been associated with shorter operation time, fewer perforations and less postoperative abdominal pain and nausea compared to electrocautery [188–190]. However, the ultrasonic dissector is more expensive and monopolar electrocautery is still the instrument of choice for most surgeons. It remains unknown whether ultrasonic dissection might be preferable in patients with acute cholecystitis.

1.10.4 The direction of the dissection

At the beginning of the laparoscopic era, many surgeons attempted to replicate the open technique, starting from the top of the gallbladder. This is called the Fundus-First, Dome-Down or Fundus-Down technique. However, it can be technically demanding to complete the dissection before dividing the cystic duct and cystic artery and the risk for injury to the greater vessel in the initial part of the learning curve is relatively high [191]. The traditional approach in laparoscopic cholecystectomy is to start the dissection in the triangle of Calot and dissect the gallbladder towards the top. However, the fundus-first approach remains in use. One Swedish hospital, Sundsvall, has developed expertise in the fundus-first technique with ultrasonic dissection. They have demonstrated shorter operating times, less pain and nausea, and shorter postoperative sick leave with ultrasonic dissection compared to monopolar electrocautery [192]. Other studies demonstrate less blood loss, fewer gallbladder perforations, and fewer complications [190, 193, 194]. However,

increased instrument costs and a reputation from early studies that fundus-first increases the risk for severe bile duct injury are the main arguments against routine use [195]. Nevertheless, many surgeons consider the fundus-first approach as a complimentary technique which can be useful in complicated cases [196].

1.10.5 Strategies in case of difficult cholecystectomies

When the anatomy is unclear, the inflammation severe, or when continuing the dissection is considered too dangerous, it is important to consider alternative solutions. The fundus-first approach might be useful in some cases, but if the inflammation in the neck of the gallbladder is severe, the difficulty remains. It is useful to shift between available tools such as graspers or suction devices for hydro-dissection; to use compresses in case of bleeding and narrow condition, and additional ports for better access. Haemostatic agents can help stop bleeding [197]. More hands, especially experienced ones, are a key to success. Subtotal cholecystectomy can be an option, in which only a part of the gallbladder is removed and the bottom of the gallbladder is left in situ [198]. Nevertheless, the laparoscopic approach is sometimes not sufficient. Conversion to open surgery is an alternative, in which manual dissection might aid in identifying the structures. A bail-out solution might be the right decision if the gallbladder can be left intact without iatrogenic lesions. In other cases, drainage and a conservative approach might be considered. Sometimes a laparoscopic approach is contraindicated from the start: in cases of lack of surgeon expertise, lack of equipment, untreated coagulopathy, extensive adhesions, advanced cirrhosis and liver failure and suspected gallbladder cancer [69]. In some of these cases, a conservative approach with antibiotic treatment can be the safest choice [199]. The most difficult decision in surgery is often when not to operate.

1.10.6 SAGES strategies for safer surgery

The Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) have online courses and recommendations based on expertise gathered within gallstone surgery [69, 200]. They have suggested six strategies to minimize the risk of a bile duct injury:

1. Strive for the critical view of safety (CSV) for identification of the important structures.
2. The surgeon should be aware of the possibility of abberant bile ducts and anatomical variations of the bile duct system.
3. Use cholangiography or other alternatives for intraoperative imaging of the billiary tree.
4. Take an intraoperative “moment-pause” before dividing any major structures to verify the anatomy and the CVS view.
5. Recognize when approaching dangerous zones and stop the dissection. If a CVS is hard to achieve or if complicating factors hinder the advancement of the dissection, consider alternative aproaches such as subtotal cholecystectomy, conversion to open surgery or a bail-out solution, often with drainage.
6. Get help from another surgeon in case of difficulty or uncertainty.

1.11 THE "SO WHAT?" OF THIS THESIS

When writing a thesis, one often hears an important question: What is the *so what* of the thesis? In other words: Why is this research important? Let us go back to Arne. His questions illustrate why this research is important.

Why did you wait so long before operating?

Even if all guidelines and most research state that patients with acute cholecystitis profit from an early operation, patients are still waiting too long due to lack of resources. We still do not know if it matters whether we operate on day one or two, or if it is acceptable to wait even longer. *When is the optimal timing of surgery for patients with acute cholecystitis?*

Do you perform a lot of gallstone operations at this hospital?

Evidence suggests that hospital and surgeon volumes are important in complicated procedures, as for cancer surgery. It is less certain whether volume matters in less complicated procedures like gallstone surgery. *Does the operative volume of cholecystectomies impact surgical outcomes?*

Is it unusual to be a female surgeon performing gallstone surgery?

Female surgeons are still in the minority worldwide. Female and male physicians practice medicine differently but it is less clear whether female and male surgeons have different results. *Do female and male surgeons' outcomes differ in cholecystectomy?*

Was it difficult to learn how to use the new instrument in the study?

Ultrasonic fundus-first is an alternative to traditional electrocautery dissection in cholecystectomy. There are some doubts about the safety of the instrument. *Is ultrasonic fundus-first dissection easy and safe during the learning curve?*

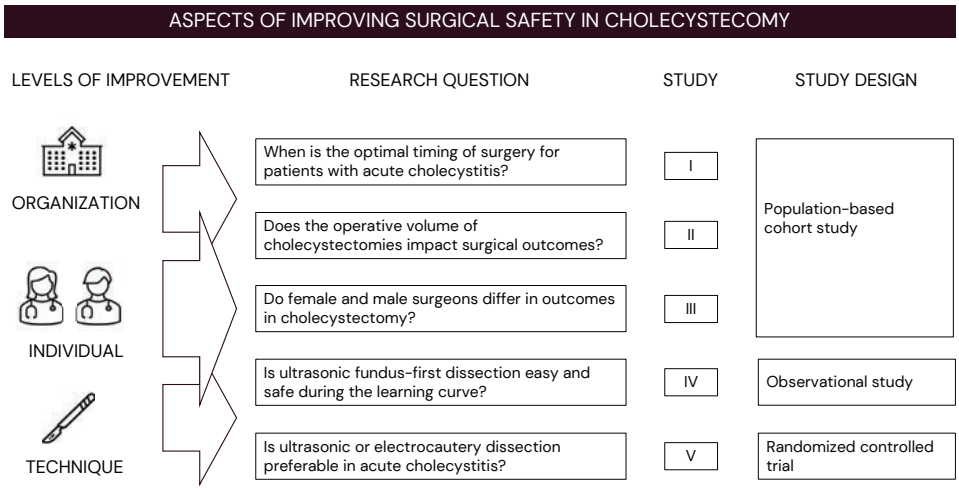
Which instrument do you think is best for patients like me, with gallbladder inflammation?

Evidence indicates that ultrasonic dissection is faster, causes less bleeding and less pain and nausea for patients in elective operations but we do not know whether it is more favourable in acute cholecystitis. *Is ultrasonic or electrocautery dissection preferable in acute cholecystitis?*

These questions will be answered and further discussed in this thesis.

2 RESEARCH QUESTIONS AND AIMS

The overarching aim of this thesis is to study gallstone disease and its most common complication, acute cholecystitis. All five papers included in this thesis are related to each other and focus on different aspects of surgical safety in cholecystectomy. Three levels are discussed: organization, the individual surgeon, and technique. An overview of the research questions and study designs is illustrated below.



The specific aim for each paper was:

PAPER I – THE SOONER THE BETTER
The aim of this study was to analyse how the timing of surgery after hospital admission for acute cholecystitis affects intra- and postoperative complication rates.

PAPER II – CASE VOLUME
The aim of this study was to investigate whether the surgeon's and hospital's annual operative cholecystectomy volume has an impact on surgical outcomes.

PAPER III – GENDER IN SURGERY
The aim of this study was to determine whether female and male surgeons differ in operating time and outcomes in elective and acute cholecystectomy.

PAPER IV – LEFFE
The aim of this study was to evaluate the learning curve for ultrasonic fundus-first dissection in elective laparoscopic cholecystectomy, focusing on dissection time and surgical safety, in terms of the intra- and postoperative complication rates.

PAPER V – SONOCHOL
The aim of this study was to investigate whether ultrasonic dissection might be an alternative to electrocautery dissection in patients with acute cholecystitis.

3 MATERIALS AND METHODS

3.1 INTRODUCTION TO THE METHODOLOGY

The Swedish Registry of Gallstone Surgery and Endoscopic Retrograde Cholangiopancreatography (GallRiks) plays an important role in all five papers included in this thesis. PAPERS I-III are registry-based studies in which GallRiks data are the main source of information. In PAPER IV-V, GallRiks data are used to complement the studies' unique Case Report Forms (CRFs). In our studies, we use the term *sex* for biological factors and *gender* when the biological sex is unknown or when we refer to attitudes and behavioral factors. This is in line with recommendations from most publishers. However, the use of the terms varies [201]. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines were used to structure the manuscripts in the observational studies, PAPERS I-IV [202]. In the randomized controlled trial, PAPER V, we used the CONSORT guidelines [203]. The clinical trials, PAPERS IV-V, were registered on https://clinicaltrials.gov (NCT03154164 and NCT03014817).

3.2 GALLRIKS

GallRiks is one of one hundred different quality registries in Sweden [204]. The registry is well-known to all surgeons performing cholecystectomies in Sweden. It was founded in May 2005 as a collaboration between the Swedish National Board of Health and Welfare, the Swedish Surgical Association and the Swedish Society of Laparoscopic Surgery [205]. The goal of the register is to aid in obtaining a high quality of care, or more specifically, evidence-based, individualized, available, efficient, safe and risk-minimizing health care for patients treated for gallstone diseases in Sweden [205].

Approximately 25,000 procedures are registered annually (14,984 cholecystectomies and 9,981 ERCP procedures in 2022) [39]. National coverage is 94.5% with a follow-up frequency of 97% [39]. Swedish registries are classified annually on a four-level scale based on pre-set criteria. For a long time, GallRiks has been a level 1 registry but this year, it was put onto level 2 [204]. GallRiks board members are currently working with the changes needed to retrieve level 1 classification. Nevertheless, GallRiks is a well-functioning registry. It has been used for quality control and to assess highly relevant research questions since its inauguration in 2005. Some examples are the importance of intraoperative cholangiography, recommendations for antibiotic and thrombosis prevention in cholecystectomy, and a detailed description of the registry [96, 97, 100, 103, 106]. The register is web-based, and the operating surgeon registers the cholecystectomy or ERCP as soon as possible after the procedure, preferably online in the operating room. The intraoperative registration includes patient characteristics, information about the surgical procedure and the intraoperative complication rate. A local coordinator completes the registration with postoperative complications in a 30-day follow-up, based on medical records. The 30-day mortality rate is retrieved from the National Population Registry. The validity of data is regularly checked by independent reviewers who visit the registering hospitals, if possible, at least every third year. The validation has shown high completeness and correctness without failure to report serious adverse events [206]. The severity of complications is graded with the Clavien-Dindo classification [114].

3.3 PAPER I – THE SOONER, THE BETTER

The Sooner, the Better? The importance of Optimal Timing of Cholecystectomy in Acute Cholecystitis: data from the National Swedish Registry for Gallstone Surgery, GallRiks

Study design

This study was a population-based cohort study of patients who underwent surgery for acute cholecystitis. (In the paper it is described as a population-based, nested case control study.) The primary endpoint was a composite of different surgical outcomes.

Participants

All elective and acute cholecystectomies registered in GallRiks between January 1, 2006, and December 31, 2014, were included in the cohort. Cholecystectomies with an incomplete 30-day follow-up and those performed with the indication of acute pancreatitis, malignancy or as a part of major surgery, were excluded.

Data sources and Variables

The GallRiks dataset included information on patient characteristics, surgical technique, antibiotics, length of hospital stay, information about intraoperative adverse events (bleeding demanding intervention, bile duct injury, gut perforation, or any other reason for the surgery to be terminated prematurely) and postoperative adverse events (all complications during the first 30 days) and 30- and 90-day mortality. The operations were divided into six groups depending on the timing of the surgery, ranging from admission to five or more days later. The association between the surgical timing and the outcomes of intraoperative adverse events, intraoperative bleeding, bile duct Injury, postoperative adverse events, 30-day mortality and 90-day mortality were analysed.

Statistical methods

Patient- and procedure-related variables in patients with and without cholecystitis were compared using Pearson's chi-square test and presented in contingency tables with two-sided P-values. Multivariable logistic regression analysis was used to compare patients with and without acute cholecystitis for different outcomes. A similar model was used to investigate the association between the timing of the operation in patients with acute cholecystitis and the risk for adverse events. The group with the longest delay, i.e., ≥ 5 days, was used as reference in the analysis. Identified confounders included in the analyses were the patient's age, gender, ASA classification, acute/elective surgery, laparoscopic/open surgery, indication for surgery and a previous history of acute cholecystitis. The associations were presented as odds ratios (OR) with 95% Confidence Intervals (CI) and p-values. Statistical analysis was performed with JMP 12.1.0 (SAS Institute, Inc., Cary, NC, USA).

3.4 PAPERS II–III – CASE VOLUME and GENDER IN SURGERY

Relationship between surgical volume and outcomes in elective and acute cholecystectomy: a nationwide, observational study

Differences in Cholecystectomy Outcomes and Operating Time Between Male and Female Surgeons in Sweden

Study design

Both studies are population-based cohort studies on patients who underwent elective and acute cholecystectomy. Several endpoints were used in PAPER II including a composite of surgical complications and operating time. In PAPER III, the primary endpoint was surgical complications.

Participants

PAPERS II and III are based on the same original cohort, with some modifications. All open and laparoscopic cholecystectomies registered in GallRiks between 2006 and 2019 were included in both studies. Data from patients operated on due to major malignancy and as a part of more extensive procedures were excluded from the retrieved data set. In both studies, procedures from the first year (2006) were excluded from the final analysis since they lacked information about the annual volumes of the surgeons. In Paper III, we also excluded patients with malignancy or polyps, procedures with unknown indication, and procedures with unknown gender of the lead surgeon.

Data sources and variables

The final data set included information about patient characteristics, surgery-related parameters, and intra- and postoperative adverse events. GallRiks does not include data about the surgeon's gender. This information was retrieved by means of a two-step data retrieval method. In the first step, we received a list of the names of all participating surgeons. The surgeon's gender was deduced from the surgeon's name. The completed list was returned to the registry holder who merged the gender data into the final data set, using each surgeon's unique identification code. Annual volumes were calculated from the number of procedures performed in the year preceding each cholecystectomy. To facilitate the analysis and presentation of data, the procedures were categorized into four subgroups, based on volume-based quartiles. A cut-off between quartiles 2 and 3 was set to define low and high volume. In PAPER II we analysed the association between the hospital's and surgeon's annual volumes and operating time, surgical complications (a composite of bile duct injury, significant bleeding, visceral perforation, bile leakage and abscess), bile duct injury, conversion to open surgery and 30-day mortality. In PAPER III, the association between the surgeon's gender and different outcomes was analysed. The primary analysis included surgical complications while secondary outcome analyses included operating time, total complications, open surgery or conversion, length of stay ≥ days and 30-day mortality.

Statistical methods

In PAPER II, the highest volume group for the hospital and surgeon was used as reference in the analyses. In PAPER III, female surgeons were used as reference in the analyses. Patient demographics were presented in contingency tables. In both papers, the associations between volume/gender and dichotomous outcomes such as complications, conversion and mortality were calculated with generalized estimating equations, with an independent correlation structure and robust standard errors. The associations were presented as OR, with 95% CI and p-values. The associations between volume/gender and operating time were calculated with mixed linear model analysis with volume/gender and identified confounders as fixed effects and the intercept of the surgeon nested in hospital as random effects. The results were presented as mean difference in time (minutes) with 95% CI and p-values. In PAPER II, the patient's age, gender, and ASA classification were included as confounders. In PAPER III, we also added the hospital type, previous history of cholecystitis, the surgeon's annual volume (from PAPER II) and the number of days from hospital admission to surgery for acute procedures. In PAPER II, spline diagrams were used to further illustrate these relationships. Statistical analysis was performed with SPSS statistics for Macintosh (Version 28.0. IBM Corp, Armonk, NY, USA).

3.5 PAPER IV – LEFFE

Learning by doing: an observational study of the learning curve for ultrasonic fundus-first dissection in elective cholecystectomy

Study design

Observational study of the learning curve for ultrasonic fundus-first dissection. The primary endpoint was dissection time.

Participants

Twenty-one surgeons from nine Swedish hospitals participated in the study. Recruitment was based on a general interest to participate. The participating surgeons were residents or specialists who could perform laparoscopic cholecystectomies independently with the traditional electrocautery technique. The surgeons had no previous experience of ultrasonic fundus-first dissection in gallstone surgery, but some of them had used the instrument in other laparoscopic procedures, such as bariatric surgery or hernia surgery. To guarantee patient safety, all surgeons participated in a mandatory day-long education session with live demonstrations and technical advice, but no practical training. Those who entered the study at a later stage were requested to have assisted in procedures with ultrasonic fundus-first dissection to an extent that equalled the education. The participants' previous experience of gallstone surgery and of the ultrasonic instrument were recorded before the start of the study. Patients >15 years of age scheduled for an elective cholecystectomy without laboratory or radiological signs of cholecystitis were eligible for the study. The final decision on inclusion was made intra-operatively after inspection of the gallbladder. The participating surgeons performed fifteen operations each.

Surgical technique

A laparoscopic cholecystectomy was performed according to a standardized protocol. As an additional safety measure, the dissection started by marking the peritoneum where the cystic duct was anticipated to enter the gallbladder. Thereafter, the fundus-first dissection was initiated. The ultrasonic Harmonic ACE + (Ethicon Endosurgery (Europe) GmbH, Norderstedt, Germany) instrument was used in the study.

Data sources and variables

Data were collected from several different sources and organized by a study ID.

1. *Case record form (CRF):* Including data about the surgeon's previous experience, operating times for different time intervals and the surgeon's self-assessment of performance and difficulty.

2. *GallRiks:* Including patient characteristics, operation-specific variables and the intra- and postoperative complication rate.

3. *Video recordings:* Videos numbers 1, 5, 10, 14 and 15 for each surgeon were sent for external evaluation by two out of three external reviewers with extensive experience of the fundus-first technique. The evaluators graded each minute of the dissection

according to error definitions by Seymour [207, 208]. Seven levels were assessed: lack of progress, gallbladder injury, liver injury, incorrect plane of dissection, burning of non-target tissue, tearing of tissue and instrument out of view. The assessors also graded the level of difficulty and commented on the surgical technique.

4. *Evaluation form:* A questionnaire was sent to all participants so that they could share experiences from the study and the technique.

Procedural steps

The operations were divided into five different procedural steps. The operating time as well as the level of difficulty were estimated for each procedural step. A numerical scale from 1 (very easy) to 100 (very difficult) was used for the difficulty and 1 (poor) and 100 (excellent) for the level of performance. The surgeons received feed-back after finishing their participation with the grades and comments from the video assessment.

TIME INTERVALS IN PAPER IV		
1	*Start*	Time from skin incision to the marking of the peritoneal margin
2	*Dissection*	Fundus-first dissection of the gallbladder, from marking the peritoneum, until placement of the first clip before the cholangiography
3	*Cholangiography*	Cholangiography
4	*Finish*	Haemostasis, removal of the gallbladder, remaining blood and bile, and fascia and skin closure
5	*Other*	Other procedures such as ERCP, hernia suture etc.
6	*Total*	Total time/difficulty/performance

Statistical methods

The demographics of participating surgeons and patients were presented in contingency tables. Dissection time was used in the analysis instead of total time since this was deemed to better reflect the operating technique. The relationship between dissection time and the procedural number of orders was analysed with multivariable linear regression modelling, adjusting for identified confounders. These were the patient's age, gender, BMI, the surgeon's self-assessed level of difficulty and ongoing cholecystitis. The results were presented as unstandardized B-values, with 95% confidence intervals and p-values. The learning curves were also visualised in individual line charts with logarithmic transformation of times for simpler presentation. The video assessments were analysed for interobserver reliability by using intra-class correlation between the observer's scores of the different error definitions. Spearman's correlation was used to assess the possible association between the video-assessment scores and the procedural numbers. Statistical analyses were performed with SPSS statistics for Windows (Version 26.0. IBM Corp, Armonk, NY, USA).

3.6 PAPER V – SONOCHOL

Ultrasonic dissection in laparoscopic cholecystectomy for acute cholecystitis, a randomized controlled trial

Study design

A randomized, multicentre, parallel-group, double-blind, controlled trial on patients with acute cholecystitis who underwent surgery with electrocautery or ultrasonic dissection. The primary endpoint was the total complication rate.

Participants

Eligible patients were patients ≥ 18 years old with mild or moderate acute cholecystitis according to the Tokyo Guidelines, with a symptom duration of ≤7 days. Exclusion criteria were (1) ASA score ≥4, (2) severe cholecystitis with multi-organ failure (Grade III) according to the Tokyo Guidelines, (3) previous major upper abdominal surgery, (4) preoperative gallbladder drainage, (5) signs of other acute or chronic abdominal diseases, (6) pregnancy, and (7) inability to understand instructions in Swedish. To be certified as a participating surgeon, experience of both techniques was needed. This could be demonstrated either by participation in the pilot study (PAPER IV) or by a video recording assessing the performance.

Randomization

Randomization of patients was performed by the operating surgeon online after induction of anaesthesia. Patients were randomly assigned to either traditional electrocautery dissection or ultrasonic dissection with a 1:1 allocation by a computer-generated randomization sequence. Permuted blocks of 4 to 6 were used, within predefined limits, stratified by centre. The study arm allocation was concealed from the patient, postoperative care providers and during follow-up. The allocated instrument was not noted in the medical records.

Procedure

The duration of symptoms (days) and the Tokyo severity grade were registered at inclusion. Patients received a diary for pre- and postoperative registration of pain and nausea, quality of life (EQ-5D-5L) and intake of pain medications. Surgery was performed as early as the local circumstances allowed. A standardized laparoscopic cholecystectomy was performed in accordance with the study protocol. Surgeons strove to achieve a critical view of safety. The ultrasonic instrument Harmonic HD1000i Shears™ (Ethicon Endosurgery [Europe] GmbH, Norderstedt, Germany) or the local electrocautery devise was used. The direction of the dissection was not predefined, and the surgeon chose the most appropriate technique based on preference, anatomical variations, and severity of inflammation. A CRF was completed at the end of the operation. The CRF included information about the surgeon's perceived level of difficulty (1 = very easy, 100 = very difficult), information about haemostatic agents, estimated amount of bleeding, and change of technique. Postoperative care was conducted according to local routines. Laboratory tests were taken before surgery and 24 hours postoperatively, or earlier at discharge. GallRiks was used to complement data on

patient demographics and intra- and postoperative adverse events. An additional 30-day postoperative follow-up was performed by a research nurse. The follow-up included information about adverse events, sick leave, and other subjective values.

Outcomes

The primary endpoint was the total complication rate including all intra- and postoperatively registered complications during the first 30 postoperative days. Secondary outcomes were operating time, use of haemostatic agents, length of stay (LOS), readmission, sick leave, quality of life (EQ-5D-5L) (preoperatively and after one week), level of pain and nausea (preoperatively and the first seven postoperative days) and systemic signs of inflammation (pre- and 24 hours postoperatively).

Power calculation

The power calculation assumed that ultrasonic dissection reduced the total complication rate from 15% to 5%. To detect a significant difference with a power of 80% at the $p<0.05$ level, a total of 141 patients would be needed in each group. To adjust for dropouts and patients lost to follow-up, the study was conducted with the aim including 300 patients.

Statistical methods

Eligible patients were all patients undergoing surgery for acute cholecystitis at the participating centres, during the inclusion period. Differences in characteristics between the study population were analysed with Pearson Chi-square test for categorical variables and independent t-test or Mann-Whitney test for continuous variables. Primary and secondary outcomes were analysed as intention-to-treat. The primary outcome, total complication rate, was analysed using logistic generalized estimated equations (GEE) with exchangeable correlation structures and robust standard errors. We chose the GEE model to avoid bias related to clustering of procedures performed by individual surgeons. The results were presented as risk difference (RD). Secondary outcome analysis was performed with a similar GEE model, independent t-test, or Mann-Whitney U-test, when appropriate. A two-sided p-value of <0.05 was considered significant. Statistical analysis was performed with SPSS statistics for Macintosh (Version 28.0. IBM Corp, Armonk, NY, USA).

3.7 ETHICAL CONSIDERATIONS

All five papers in this study were approved by the Regional Ethics Review Board in Stockholm or Uppsala, Sweden. The papers' different study designs and perspectives required different ethical considerations. Some thoughts and reflections follow below.

POPULATION-BASED COHORT STUDIES

PAPERS I–III are register-based studies based solely on GallRiks data. In most cases, registry data are de-identified and there is rarely an ethical issue with these studies. However, there are some things to consider. Patients are informed of their upcoming registration in GallRiks when they are scheduled for surgery. This is usually via written information about the registry, specifying its purposes and the patient's rights. Patients always have the right to decline participation and can request to see, correct or remove data at any time (the opt-out principle) [205]. Written consent for participation is neither required nor documented. This is called a waiver of consent, granted only if the research presents a minimal risk of harm and involves no procedures for which written consent is usually required [209, 210]. Due to this we cannot know for sure that all patients in GallRiks know that they are registered and have given their approval. Patients are registered with their personal ID numbers and the registration includes health information that might be considered sensitive, such as name, gender, age, and comorbidities. Individual patient data can only be used for quality assessment at the local clinic: in research studies, the data sets are mostly de-identified. The process of retrieving data is well regulated, and information is protected by the registry holder. An ethical approval is needed for research and an application describing the project must be approved by the GallRiks board members. In cases like mine, when most of the supervisors are present or former board members of GallRiks, the application must be approved by a secondary party.

In **PAPERS I and II,** no individual information was used, and all analyses were performed on a group level. However, the data could possibly be connected to a specific patient since it includes gender, age, and operation dates. No sensitive information was presented in the final publication and individuals could not be identified. Data in registry-based cohort studies are collected and used in retrospect. The patients are informed that their data might be used in future studies, but they are not asked every time a study is approved. If written consent were needed for each research study, it would be nearly impossible to do this kind of research. The advantage of registry-based studies - namely to use large cohorts and study rare outcomes with sufficient statistical power - would disappear. In the case of cholecystectomies, the registered patients will not benefit from the research themselves since most of us only have one gallbladder. The research will, however, benefit future patents undergoing cholecystectomy and will contribute to a better understanding of the disease (the principle of benevolence).

PAPER III is also a register-based study, but it includes the variable of the surgeon's gender, which is not registered in GallRiks. To get this information, we received a list of all surgeons' names and the surgeons' gender was deduced from the given name. (GallRiks differs from other surgical registries, such as the Swedish Hernia Registry and Scandinavian Obesity Surgery Registry, which only include a code, and not the name). The list was then returned to the registry holder and integrated into the data set. This was done to assure anonymization of the surgeons, since the name connected to surgical outcomes is considered sensitive information. To receive gender data, an additional application was approved by the Regional Ethics Review Board.

CLINICAL OBSERVATIONAL COHORT STUDIES

PAPER IV is an observational study of a surgical technique. This might be an ethical issue if it were possible for the technique to worsen outcomes. In this study, the ultrasonic instrument is well-established and in general clinical use. However, the participating surgeons had no previous experience of ultrasonic fundus-first dissection in gallstone surgery, which might increase the risk of negative postoperative outcomes. Since all surgeons were previously experienced in gallstone surgery, and we clearly specified that the surgeons should choose their preferred technique in case of difficulty, we considered it ethical to do the study. Training that included live operations and technical advice, or previous experience from assisting, was compulsory for participation in the study. As an extra safety measure, we recommended that the assisting surgeon was at least a surgical resident. In the study, all data were de-identified and codes were stored in a safe place. As has been further discussed above, the study also used GallRiks data. In this case, we sent a list with the patient's unique social security numbers to the registry holder and acquired individual information. All patients gave both oral and written informed consent to participate in the study. In the publication, information was presented on a group level, apart from details regarding complications which might be referred to a specific patient.

Introducing new techniques is an interesting ethical aspect in surgery. Technology is developing very fast, and all instruments are approved for clinical use before being introduced into regular use. However, learning curve studies are rare and most instruments are implemented in clinical practice without patient consent. After anaesthesia, the patients are unaware of what is happening. They don't know whether a senior surgeon lets their apprentice operate or whether the surgeon is testing a new instrument. In this study, all participants were well informed about the two different techniques and had given written informed consent. Is this more ethically correct than clinical practice in general? We used video recordings to evaluate the surgical technique. The films were reviewed in retrospect. Continuous video evaluation throughout the study could have been a way to further assess safety. PAPER IV was also a pilot study to evaluate safety and decrease potential risks of ultrasonic dissection for PAPER V.

RANDOMIZED CONTROLLED TRIALS

PAPER V was designed as a randomized controlled trial, in accordance with the ethical standards of the Declaration of Helsinki and good clinical practice guidelines [211]. It was while discussing ethical aspects of the RCT that we came up with the idea of doing a learning curve study. How do you guarantee surgical safety for patients when you randomize between two instruments, when most surgeons have experience of only one technique? In this case, PAPER IV was the answer. The first application to the Ethics Review Board was submitted very early during the process of designing PAPER V. Before the start of the study, the protocol was edited extensively, and an additional application was sent to the Ethics Review Board and approved.

When planning an interventional study, it is important to consider both risks and benefits. The idea behind our study was based on favourable elective results from the surgeons in Sundsvall [212], together with a hypothesis that the ultrasonic dissector's capacities might be especially useful in acute surgery. The risks were considered low, or at least no higher than the standard traditional treatment, and the benefits were likely substantial. All participating surgeons had previous experience of at least fifteen operations with the ultrasonic device or could prove their instrument handling capacity by sending a video for assessment and approval. In comparison, the surgeons in PAPER V had more experience of handling the instrument in gallstone surgery, compared to the surgeons in PAPER IV.

Only patients who could understand information and give written consent in Swedish were included in the study. The informed consent used easily understood language and included images of both techniques. The diary was tested on five patients beforehand, and explanations were added when needed. Patients and postoperative caregivers were blinded to the technique. The allocated instrument was not noted in the medical records, which are accessible online for patients in Sweden. This was considered important since many patients expressed an expectation that the "more modern" instrument would be better than the old one. All data were stored separately and linked together before analysis. Unique social security numbers were used for randomization, and to access GallRiks data, but these were safely stored.

When designing PAPER V, we had difficulties in setting the primary outcome. We discussed the variables of pain and nausea, but refrained from using them due to the difficulties we could foresee in standardizing anaesthesia and postoperative medications in a multicentre setting. We considered the primary endpoint of total complications to be of great benefit for the patient as well as of clinical interest. In retrospect, the power calculation in this study was too optimistic. Nevertheless, we demonstrated equal complication rates. Even with a less optimistic power calculation, it is unlikely that we would have reached statistical significance in a randomized clinical trial. This is one example where registry-based studies could have been useful. Unfortunately, the instrument used for dissection is not a variable in GallRiks.

4 RESULTS

4.1 PAPER I – THE SOONER THE BETTER

LEVEL	STUDY	MAIN RESULTS
 ORGANIZATION	I	▪ 84,108 patients were analysed, 18.1% with acute cholecystitis (AC) and 81.9% without cholecystitis. ▪ Patients with AC had higher rates of intra- and postoperative complications, compared to patients without AC. ▪ 78.4% of the patients with AC underwent surgery within 3 days. ▪ Intraoperative adverse events for patients with AC were lowest for patients who underwent surgery on day 1 or 2. ▪ The bile duct injury rate was lowest on admission day. ▪ The 30- and 90-day mortality was lowest day 1.

A total of 100,258 cholecystectomies were registered in GallRiks between January 1, 2006, and December 31, 2014. After exclusions, 87,108 patients remained for analysis, of whom 71,348 (81.9%) had no acute cholecystitis (AC) and 15,760 (18.1%) had AC. Overall, patients with AC had significantly higher rates of intraoperative adverse events (OR 1.23, 95% CI 1.12-1.35) and postoperative adverse events (OR 1.38, 95% CI 1.26-1.51), compared to patients without AC. Conversion rates were 20.12% for patients with AC and 5.26% for patients without AC. No significant difference in 30- or 90-day mortality was demonstrated between the two groups in the multivariable analysis.

Main results

Of all patients who underwent surgery for an AC, 11.9% had their operation on the day of admission, 39.2% on the first day and 27.3% on the second day after hospital admission. The rate of bile duct injury was lowest (0.17%) when the operation took place on the day of admission (OR 0.19, 95% CI 0.04-0.68). The bile duct injury rate increased gradually with increasing waiting time and reached as high as 0.93% on day ≥ 5. Intraoperative adverse events were lowest for patients operated on day one (OR 0.67, 95% CI 0.49-0.96) or day two (OR 0.66, 95% CI 0.47-0.95). No significant difference in the rate of intraoperative bleedings could be seen between the groups. The risk of postoperative adverse events was lower when a patient underwent surgery within 4 days of hospital admission (OR 0.61, 95% CI 0.45-0.82). Surgery on day ≥ 5 is used as reference in all analyses.

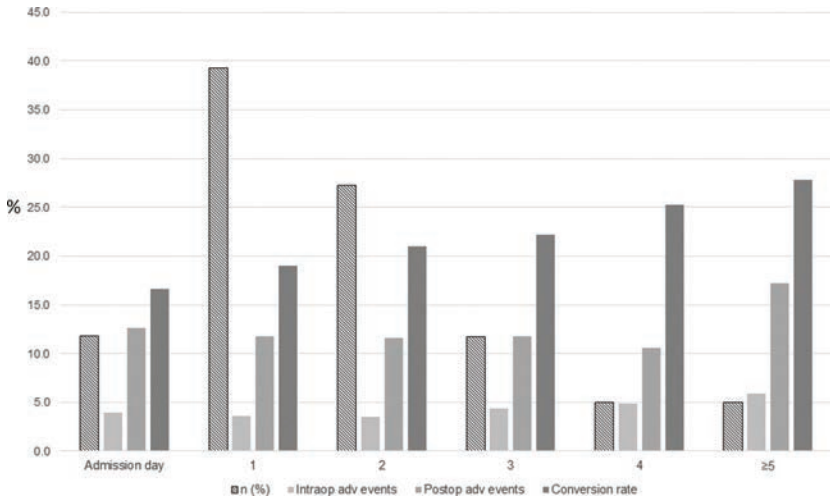


Figure 4.1 Adverse events in relation to the timing of surgery for acute cholecystitis

The conversion rate increased gradually from 16.6% on admission day to 27.8% for patients operated on ≥ 5 days. The 30- and 90-day mortality was lowest for patients who underwent surgery on day one after hospital admission (30-day OR 0.40, 95% CI 0.18-0.93) v/s (90-day OR 0.28, 95% CI 0.16-0.51). The mortality rate increased gradually for each day that passed. For most outcomes the rate of intra- and postoperative adverse events, including mortality, seemed to be lowest on days one and two after hospital admission. Overall, operations on admission day had a slightly higher rate of adverse events compared to patients who had their surgery on days one and two.

4.2 PAPER II – CASE VOLUME

LEVEL	STUDY	MAIN RESULTS
 ORGANIZATION  INDIVIDUAL	II	▪ 154,934 patients were analysed, 65.3% elective and 34.7% acute procedures. ▪ Low volume was defined as <20 operations/year for surgeons and <211 operations/year for hospitals. ▪ Operating time and conversion rates decreased with increasing volumes for both the individual surgeon and the hospital. ▪ The surgical complication rate was higher for surgeons with volumes between 10-33 operations in elective surgery. ▪ Bile duct injuries were more frequently caused by low-volume surgeons in elective surgery. ▪ Low-volume hospitals had significantly more bile duct injuries in both elective and acute surgery and a higher 30-day mortality in the acute setting.

In total, 162,472 cholecystectomies were registered in GallRiks between January 1, 2006, and December 31, 2019. Procedures from 2006 were excluded after annual volumes had been calculated, leaving 154,934 patients for analysis: 101,221 (65.3%) elective and 53,713 (34.7%) acute operations. The procedures were performed by 2,637 surgeons at 89 registering units. The procedures were divided into volume-based quartiles on the individual level (≤9, 10–19, 20–33, and >33 operations/year) and hospital level (≤136, 137–210, 211–305, and >305 operations/year). The mean (SD) number of operations was 24 (23) for the individual surgeon and 234 (127) for the hospital. To facilitate the presentation of the results, a cut-off for low and high volume was set between volume quartiles 2 and 3. Consequently, the definition of low volume was <20 operations/year for surgeons and <211 operations/year for hospitals.

Main results

Operating time decreased significantly with increasing volumes in elective and acute surgery, for both the individual surgeon and the hospital. The rate of surgical complications was significantly higher for surgeons with annual volumes between 10-19 (OR 1.15, 95% CI 1.01-1.31) and 20-33 operations (OR 1.16, 95% CI 1.02-1.31) in elective surgery, but no significant difference was seen for the lowest quartile, or at the hospital level. Bile duct injuries were more frequently caused by low-volume surgeons in elective surgery (OR 1.58, 95% CI 1.15-2.17). Low-volume hospitals had significantly more bile duct injuries in both elective (OR 1.97, 95% CI 1.39-2.81) and acute (OR 1.96, 95% CI 1.25-2.94) procedures. Conversion rates decreased significantly with increasing volumes in both elective and acute procedures, for both the individual surgeon and the hospital. No difference in 30-day mortality could be demonstrated between the volume groups on the individual level. However, low-volume hospitals had significantly higher 30-day mortality in the acute setting (OR 2.09, 95% CI 1.09-3.98).

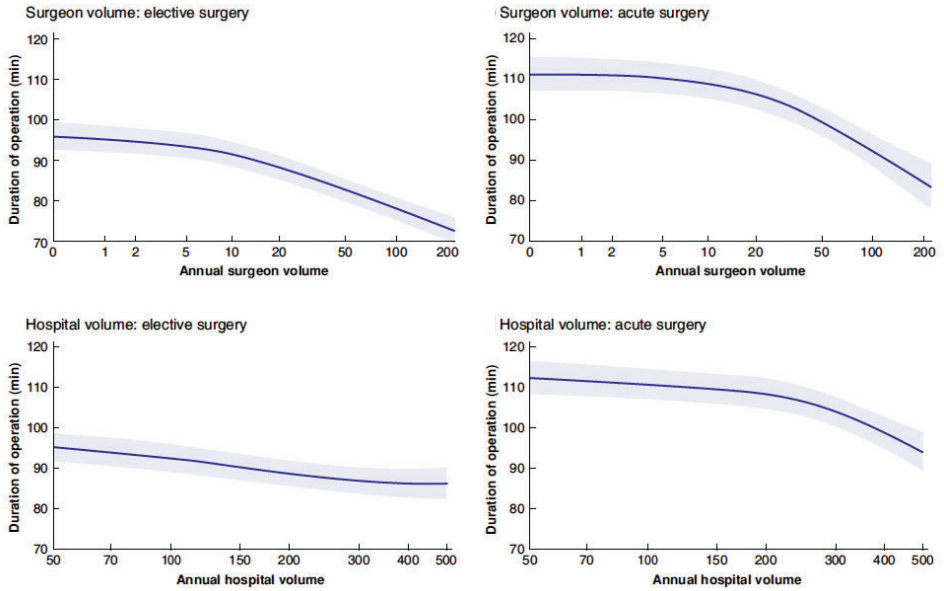


Figure 4.2a Spline functions for mean duration of surgery and surgeon and hospital volumes, in elective and acute operations

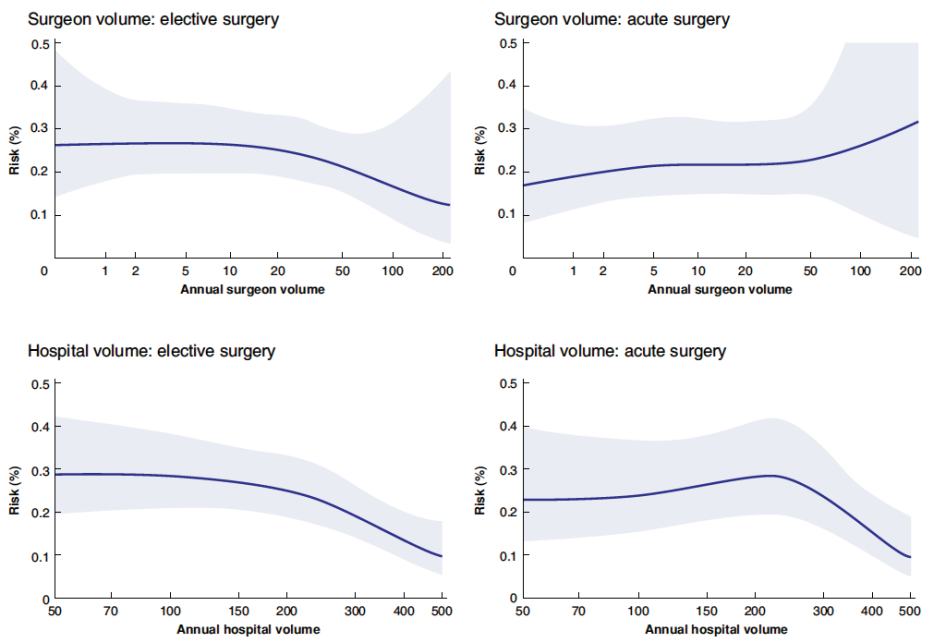


Figure 4.2b Spline functions for surgical complications and surgeon and hospital volumes, in elective and acute operations

4.3 PAPER III – GENDER IN SURGERY

LEVEL	STUDY	MAIN RESULTS
 INDIVIDUAL	III	▪ 150,509 patients were analysed, 64.9% elective and 35.1% acute operations, operated on by 2,553 surgeons, of whom 33.3% were female and 67.7% male. ▪ Female surgeons worked more frequently at universities and private clinics and had lower annual volumes. ▪ Female surgeons had fewer surgical and total complications, including fewer bile duct injuries in elective surgery. ▪ Female surgeons converted less frequently to open surgery in acute surgery and their patients had shorter hospital stays. ▪ No difference was seen in 30-day mortality.

In this study, 162,472 patients were registered in GallRiks from January 1, 2006 to December 31, 2019. After exclusion, 150,509 patients remained for analysis. Of these 97,755 (64.9%) were elective and 52,754 (35.1%) were acute cholecystectomies. In total, 2,553 surgeons participated, 849 (33.3%) female and 1,704 (67.7%) male surgeons. The proportion of female surgeons increased during the study period. Female surgeons worked more frequently at universities and private clinics and performed slightly more elective procedures. Female surgeons performed fewer cholecystectomies per year compared to male surgeons. The annual operating volume (SD) was 18 (15) operations/year for female surgeons and 26 (24) operations/year for male surgeons. More female surgeons were low-volume surgeons (≤9 operations per year) and fewer were high-volume surgeons (>33 operations per year).

Main results

Male surgeons had more surgical complications (bile duct injury, bile leakage, visceral perforation, bleeding, and abscesses) in both elective (OR 1.39, 95% CI 1.25-1.54) and acute (OR 1.17, 95% CI 1.04-1.32) procedures. The risk for causing a severe bile duct injury was higher for male surgeons in elective cholecystectomies (OR 1.69, 95% CI 1.22-2.34) but no significant difference was seen in acute operations. The total complication rate was also higher for male surgeons (OR 1.12, 95% CI 1.06-1.19). Female surgeons operated more slowly than male surgeons. The mean difference in operating time between female and male surgeons, after adjusting for confounding factors, was approximately 8 minutes (-7.96) for all operations: more precisely, -6.59 minutes (95% CI -8.07 to -5.10) in elective operations and -9.27 (95% CI -11.36 to -7.19) for acute operations. Patients operated on by male surgeons had longer hospital stays (≥3 days) (OR 1.21, 95% CI 1.11-1.31) and female surgeons converted to open surgery less frequently in the acute setting (OR 1.22, 95% CI 1.04-1.43). No difference in 30-day mortality could be demonstrated. In addition, male surgeons caused more significant bleedings in both elective (OR 1.66, 95% CI 1.24-2.23) and acute surgery (OR 1.60, 95% CI 1.15-2.21).

Additional analyses

During the peer-review process of PAPER III, we received a question about surgeon volume and gender. An additional analysis was not included in the publication, but I performed a subgroup analysis of surgeon gender and outcomes divided into the volume-based quartiles from PAPER II. Some outcomes are rare, and there is a loss of statistical power in some of the subgroups. However, male surgeons seem to have less favourable outcomes in gallstone surgery, despite their annual volumes.

GENERALIZED ESTIMATING EQUATION FOR DIFFERENT OUTCOMES COMPARING MALE TO FEMALE SURGEONS, DIVIDED INTO VOLUME-BASED QUARTILES

	All operations [a]		**Elective surgery [b]**		**Acute surgery [c]**	
	OR (95% CI)	**P**	**OR (95% CI)**	**P**	**OR (95% CI)**	**P**
Female surgeons	1 (Reference)	NA	1 (Reference)	NA	1 (Reference)	NA
Male surgeons						
Surgical complications[d]						
≤ 9	1.27 (1.12-1.44)	**<0.001**	1.46 (1.24-1.73)	**<0.001**	1.10 (0.93-1.30)	0.26
10-19	1.24 (1.07-1.42)	**0.003**	1.39 (1.15-1.68)	**<0.001**	1.05 (0.86-1.28)	0.62
20-33	1.44 (1.23-1.69)	**<0.001**	1.46 (1.21-1.77)	**<0.001**	1.40 (1.09-1.80)	**0.01**
>33	1.22 (1.01-1.46)	**0.035**	1.18 (0.94-1.48)	0.17	1.34 (1.00-1.80)	**0.048**
Bile duct injury[d]						
≤ 9	2.15 (1.39-3.33)	**<0.001**	2.69 (1.49-4.85)	**0.001**	1.67 (0.93-3.01)	0.085
10-19	1.34 (0.88 –2.05	0.18	1.56 (0.91-2.68)	0.10	1.01 (0.53-1.92)	0.98
20-33	1.09 (0.71-1.68)	0.68	1.12 (0.65-1.93)	0.69	1.02(0.51-2.07)	0.95
>33	2.17 (1.16-4.29)	**0.016**	1.86 (0.87-3.95)	0.11	2.80 (0.84-9.35)	0.10
Total complication rate[e]						
≤ 9	1.17 (1.08-1.28)	**<0.001**	1.24 (1.11-1.38)	**<0.001**	1.11 (0.99-1.24)	0.080
10-19	1.06 (0.96-1.17)	0.24	1.11 (0.98-1.25)	0.10	1.0 (0.87-1.15)	0.95
20-33	1.16 (1.05-1.29)	**0.005**	1.11 (0.98-1.25)	0.90	1.24 (1.05-1.46)	**0.01**
>33	1.10 (0.96-1.26)	0.19	1.07 (0.91-1.26)	0.41	1.20 (0.97-1.47)	0.09
Conversion to open surgery[d]						
≤ 9	1.40 (1.19-1.63)	**<0.001**	1.49 (1.16-1.90)	**0.002**	1.35 (1.12-1.62)	**0.001**
10-19	1.15 (0.94-1.42)	0.18	1.29 (0.95-1.74)	0.11	1.06 (0.85-1.31)	0.61
20-33	0.89 (0.64-1.22)	0.46	0.78 (0.49-1.26)	0.31	1.04 (0.79-1.36)	0.80
>33	0.95 (0.52-1.73)	0.86	0.68 (0.31-1.49)	0.34	1.66 (1.08-2.55)	**0.021**
Length of stay >3 days[f]						
≤ 9	1.29 (1.17-1.42)	**<0.001**	1.46 (1.24-1.72)	**<0.001**	1.22 (1.09-1.36)	**<0.001**
10-19	1.10 (0.97-1.24)	0.13	1.18 (0.99-1.40)	0.060	1.04 (0.91-1.20)	0.57
20-33	1.21 (1.06-1.39)	**0.006**	1.24 (1.03-1.49)	**0.023**	1.19 (1.01-1.39)	**0.034**
>33	1.24 (1.01-1.52)	**0.039**	1.26 (0.94-1.68)	0.12	1.28 (1.03-1.58)	**0.025**
30-day mortality[d]						
≤ 9	0.98 (0.54-1.77)	0.95	0.85 (0.25-2.97)	0.80	1.00 (0.51-1.98)	0.99
10-19	2.05 (0.79-5.34)	0.14	1.72 (0.37-7.98)	0.49	2.09 (0.74-5.89)	0.16
20-33	1.13 (0.37-3.45)	0.83	NA	NA	0.90 (0.29-2.80)	0.86
>33	1.02 (0.37-2.83)	0.97	1.03 (0.23-4.57)	0.97	0.93 (0.25-3.50)	0.92

[a] Adjusted for the patient's age, sex, ASA, acute/elective surgery, previous cholecystitis, hospital type, and the surgeon's annual operative volume

[b] Adjusted for the patient's age, sex, ASA, previous cholecystitis, hospital type and the surgeon's annual operative volume

[c] Adjusted for the patient's age, sex, ASA, previous cholecystitis, hospital type, the surgeon's annual operative volume and days in hospital before surgery

[d] Excluded due to missing data: all operations and elective surgery: 806, acute surgery: 1,193

[e] Excluded due to missing data: all operations and elective surgery: 4093, acute surgery 2,478

[f] Excluded due to missing data: all operations and elective surgery: 3205, acute surgery 2,229

4.4 PAPER IV – LEFFE

LEVEL	STUDY	MAIN RESULTS
INDIVIDUAL TECHNIQUE	IV	▪ In total 240 operations were analysed, by 16 surgeons. ▪ Dissection time decreased significantly during the learning curve. ▪ The total complication rate was 5.8%, including 1.3% potentially technique-related complications. ▪ The surgeon's performance level was lower in cases of more complicated procedures. ▪ No significant association between procedural level and error definitions from the video assessment could be seen.

Procedures from May 1, 2017, to December 31, 2019 were included in this study. A total of 240 operations were analysed. Sixteen out of 21 surgeons completed their 15 operations. Five surgeons from four different hospitals dropped out early and twenty-five patients were excluded intraoperatively due to acute/chronic cholecystitis (21), technical problems (1), and extensive adhesions (3).

Main results

Dissection time

The mean dissection time was 28 minutes (range 8-90). Dissection time decreased significantly over the 15 operations. Two of the 16 surgeons demonstrated no reduction in dissection time. The decrease in dissection time was more pronounced for residents who had steeper learning curves.

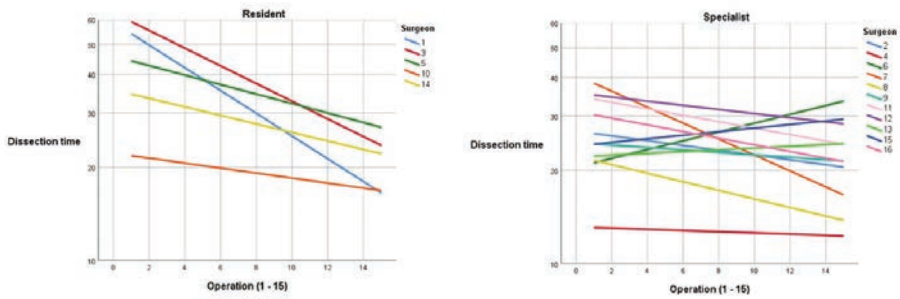


Figure 4.4 Individual learning curves of dissection time (min) for residents and specialists

The total complication rate
The complication rate was 14 (5.8%) in the study. When analysing the complications more carefully, 3 (1.3%) patients had a complication possibly associated with the technique. All three complications were caused by specialists. One patient underwent re-exploration due to intense postoperative pain, but the cause could not be identified. Two patients had postoperative bile leakage from the cystic duct. In both cases, the duct had been closed with two proximal clips. None of the 240 operations was converted to open surgery. No relationship between the procedural number and the complication rate could be found (p=0.61). The other complications were urinary infections, wound infections, unspecific postoperative symptoms, infections, or ERCP-related complications. Common bile duct stones were identified in 6 (2.5%) of the patients.

Performance level
The surgeons graded their performance level lower when the operation was graded as more complicated (p=<0.001). Since an ongoing cholecystitis might render the operation more difficult, this was added as a confounder in the analysis, but the correlation remained.

Video assessment
Ten videos were missing due to technical issues, often early during the study. When analysing associations between the two assessors and their grades, there was a high concurrence for gallbladder perforations (intra-class correlation 0.943, p<0.001). Three other categories differed significantly: the total score (0.655, p<0.001), lack of progress (0.591, p<0.001), and incorrect plane of dissection (0.517, p=0.001). No other significant concurrence could be demonstrated. No significant relationship between the procedural level and the error definitions from the video assessment could be seen.

Other findings
In 57 (23.8%) of the patients, the posterior wall of the gallbladder showed signs of an ongoing chronic 51 (21.3%) or acute 3 (1.3%) cholecystitis. For practical reasons, the time span between the first and fifteenth operations was not defined beforehand, and the mean timespan was 312 days (range 74 to 565 days). A gallbladder perforation was noted in 73 (30.4%) of the operations. Nearly half of these 35 (47.9%) occurred when the assisting surgeon lacked experience. No association between the procedural number and the gallbladder perforations could be seen. Most of the perforations occurred early relatively close to the top of the gallbladder.

4.5 PAPER V – SONOCHOL

LEVEL	STUDY	MAIN RESULTS
 TECHNIQUE	V	▪ Three hundred patients were randomly assigned to treatment, 148 to electrocautery and 152 to ultrasonic dissection. ▪ 25 surgeons participated in the study. ▪ Patients assigned to ultrasonic dissection were more often males and had a higher ASA score. ▪ No difference in total complications was demonstrated. ▪ Ultrasonic dissection reduced the need for haemostatic agents. ▪ The groups did not differ in operating time, hospital stay or readmission.

Patients were recruited between September 30, 2019 and March 22, 2023. In total, 1,359 patients with acute cholecystitis were eligible for inclusion, at eight hospitals. Patients were only recruited when participating surgeons were available. Three hundred patients were randomly assigned to treatment, with 148 patients assigned to electrocautery dissection and 152 patients assigned to ultrasonic dissection. All other randomized patients were included in the intention-to-treat analysis and assessed for the primary endpoint (n=300). The study population was older (59 ± 16 years vs. 44 ± 18 years) with similar sex distribution as those not included in the study. The study population had a lower ASA grade. The operations were performed by 25 surgeons with a median number of 7 operations per surgeon (range 1 – 38). Patients assigned to ultrasonic dissection were more often male, with a higher ASA score. At the time of inclusion, 163 (54.3%) of the patients had no previous history of gallstone-related symptoms, and 21 (7.0%) patients had a history of previous cholecystitis. The mean duration of symptoms was 3±1.5 days.

Main results

Primary outcome
The total complication rate was 27 (18.2%) in patients assigned to electrocautery, 2 (1.4%) with intraoperative and 26 (17.6%) with postoperative complications. The corresponding information in patients assigned to ultrasonic dissection was 26 (17.1%), of whom 2 (1.3%) had intraoperative and 25 (16.4%) had postoperative complications. The risk difference (RD) for total complications was 1.6% (95% CI - 7.2% to 10.4%, p=0.72).

Cross-over
Among patients assigned to electrocautery dissection, 4 (2.7%) patients were converted to open surgery and in 13 (8.7%) cases the ultrasonic device was used as a complement. This was mainly due to highly vascularized gallbladders and advanced cholecystitis. In the ultrasonic dissection group, 1 (0.7%) patient underwent conversion to open surgery, 1 (0.7%) patient underwent a subtotal cholecystectomy and in 14 (9.2%) patients, electrocautery was used as a complement. In most cases, electrocautery was only used as a complement, especially when a more precise dissection in Calot's triangle was required and the ultrasonic device was considered too blunt.

Operating time
Mean operating time was 100 min ± 38 for electrocautery and 99 min ± 42 for ultrasonic dissection (mean difference 1 min, 95% CI -8min to 10min, p=0.82).

Haemostatic agents
With electrocautery dissection, the median of estimated bleeding was 60 ml (Inter Quartile Range (IQR) 25 – 100 ml). For ultrasonic dissection, it was 50 ml (IQR 20 – 100 ml). Haemostatic agents were used in 40 (27.0%) patients assigned to electrocautery and 27 (17.8%) patients assigned to ultrasonic dissection. The risk difference was 10.6% (95% CI, 1.3% - 19.8%, P=0.025).

Hospital stay and readmission
The median postoperative hospital stay was 2 days (IQR 1 – 2 days, range 0-23) for electrocautery and 1 day (IQR 1-2 days, range 0-10) for ultrasonic dissection. No significant difference was seen between the groups (p=0.19). In total, 6 (4.1%) patients assigned to electrocautery dissection and 7 (4.6%) patients assigned to ultrasonic dissection were readmitted to hospital (p=0.82).

Other analyses
The gallbladder was accidentally perforated in 77 (52.0%) of the cases in the electrocautery group and 87 (57.2%) patients in the ultrasonic group (p=0.365). The gallbladder was also voluntarily punctured by the surgeon in 93 (62.8%) in the electrocautery group and 98 (64.5%) for ultrasonic dissection (p=0.89). This was mostly done due to gallbladder distention and because the gallbladder was difficult to grasp. A successful cholangiography was performed in 285 (95.0%) of the patients: 145 (98.0%) of the patients assigned to electrocautery and 141 (92.8%) of those assigned to ultrasonic dissection. Common bile duct stones were found in 14 (9.5%) of the electrocautery patients and 21 (13.8%) of the patients assigned to ultrasonic dissection. electrocautery patients.

5 DISCUSSION

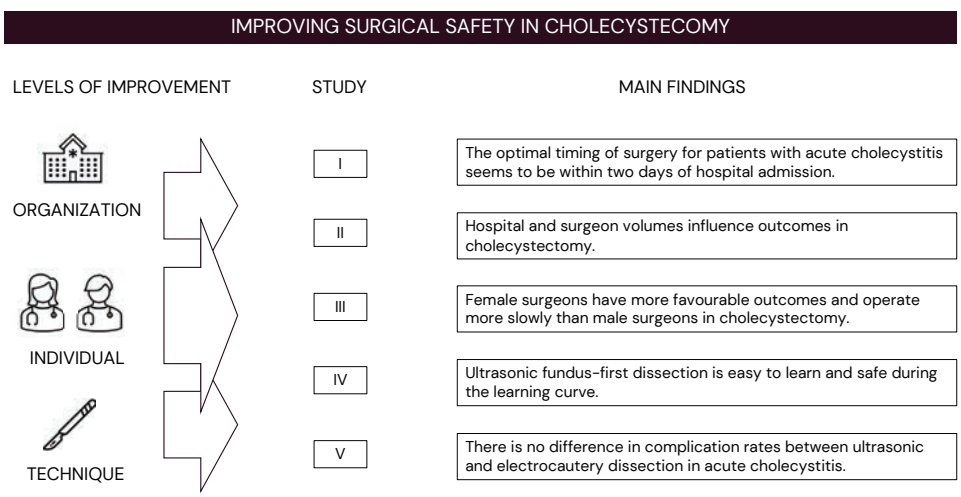
5.1 GENERAL DISCUSSION

Improving surgical safety in gallstone surgery is important because cholecystectomies are one of the most frequently performed procedures in the world. All of us are at risk for experiencing this surgery. The results in this thesis might be summarized in five personal questions:

- When do you want your acute operation?
- Do you want an experienced surgeon and do you want to be treated at a high volume unit?
- Does it matter if the surgeon is male or female?
- Do you mind if the surgeon uses ultrasonic fundus-first dissection without previous experience with the instrument?
- Which instrument should the surgeon use in acute cholecystits?

In Sweden, you are not able to choose the timing of your surgery, nor the surgeon, because it depends on many other factors. Neither will you be aware of which instrument the surgeon uses, since you are heavily asleep. (And it is a bad idea to ignore the symptoms and stay at home because you know that your acute cholecystitis profits from being operated on as soon as possible). It is the organization and the individual surgeons who must ensure high quality of care 24/7/365, everywhere in the country, and the world. Research on cholecystectomies has the potential to improve health care for many patients, since it such a common procedure. All five articles in this thesis include elaborate discussion on their respective topic. I will try not to repeat these thoughts and reflections here. I will focus on what they have in common; different aspects of surgical safety in gallstone surgery, and how our main findings might be interpreted and inserted into the broader perspective.

5.2 MAIN FINDINGS



5.3 DISCUSSION OF SURGICAL SAFETY ON THE ORGANIZATIONAL LEVEL

5.3.1 Timing of surgery in acute cholecystitis

The main finding in PAPER 1 – THE SOONER THE BETTER is that the optimal timing of surgery for patients with acute cholecystitis seems to be within two days of hospital admission. This article was published in 2016, seven years before this thesis was written, and it remains one of the biggest cohort studies published within the field. What has changed since then? Nearly all published evidence and guidelines verify our results and recommend early surgery [10, 56, 68, 70-72, 126, 213, 214]. Acute surgery is the "gold standard" and recommended treatment for patients with acute cholecystitis, just as initial conservative treatment is considered the "gold standard" for a single episode of uncomplicated biliary colic. If the patient is deemed able to tolerate surgery, the recommendation is to operate during the first hospital stay, no matter the duration of symptoms, but preferably within three days [10, 126, 213]. This recommendation includes patients who are generally at high risk for surgery (but also less probable to tolerate the conservative approach), including the elderly, patients with mild to moderate cirrhosis, and cardiac and renal diseases [71, 215, 216].

5.3.2 Do we follow the recommendations?

Despite this impressive evidence patients with acute cholecystitis still wait for surgery. In PAPER I, 78% of patients underwent surgery within two days of hospital admission. This still seems a high number today, even if we do not know the proportion of patients who were dismissed and scheduled for delayed surgery. In 2023, the Swedish health care system is struggling with limited resources, especially on the individual level. There is a lack of nursing staff, operating rooms are temporarily closed, and there are not enough beds. Malignant surgery has been centralized to university hospitals and their resources for acute benign gallstone surgery are shrinking. Consequently, operations are delayed, and patients are still discharged and scheduled for elective cholecystectomy. The Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) conducted a large systematic literature review in 2016, focusing on the treatment of cholelithiasis and acute cholecystitis. In a health economic analysis, they concluded that an increase in acute operations for acute cholecystitis from 60% to 90% would result in a reduction of three hospital days per patient, a total of 3,300 hospital days/year. This was estimated to save 26 million Swedish crowns/year [129]. PAPER I may be getting old, but its content and conclusions are still important, due to our everyday challenges. Gunnar Edlund, who assessed video recordings in PAPER IV, published a thesis about the need for acute surgery for acute cholecystitis in 1984 [217]. We are still struggling with the same problems. Let us hope that healthcare organizations will improve, and that this thesis will not be cited in the same way 40 years from now.

5.3.3 Are extended operating hours a way to faster surgery?

In our study, we do not know the exact timing of surgery. Cholecystectomies performed out of hours have been associated with a slightly increased risk for complications [218]. Other studies show shorter operating times but more conversions to open surgery, with comparable complication rates [219-221]. The high proportion of open surgeries is a common argument as to why patients with acute cholecystectomies are rarely operated on late at night [218-220]. However, performing more acute cholecystectomies at night has been suggested as a solution for faster access to surgery, especially in high volume hospitals with limited daytime resources [221]. The question is complex. Do we have high-volume surgeons available day and night, and are there resources for intraoperative common bile duct stone removal at night? A balance between what is optimal in the clinical perspective, and optimal in the practical perspective, must be achieved. Some suggest that cholecystectomies should be performed by surgeons at acute surgical units, performing all kinds of acute surgery day and night, 7 days per week [222]. The implementation of these routines in some countries has resulted in reduced conversion rates and shorter hospital stays after cholecystectomy [222, 223]. There is an ongoing debate in Sweden today about who should perform gallstone surgery, but that issue is beyond the scope of this thesis.

5.3.4 Implementing evidence-based medicine in clinical practice

There are obvious challenges in implementing evidence-based recommendations in clinical practice. This is an important issue for surgical safety on the organizational level. It is well known that implementing evidence-based medicine and guidelines might be difficult and takes time. Lack of resources and education, insufficient knowledge about the research field, and lack of motivation and incentives, are known obstacles [224]. But it is possible. A good example is the Enhanced Recovery After Surgery (ERAS) concept, a multidisciplinary approach to perioperative care which has resulted in a reduction in complications, shortened hospital stays and reduced costs for several surgical procedures [225, 226]. The Swedish National Guidelines for Gallstone-Related Diseases were published in September 2023. They recommend acute surgery for patients with acute cholecystitis, a recommendation they graded as strong, based on a medium to high level of evidence [10]. Hopefully this can further highlight the need for emergency surgery for patients with acute cholecystitis in Sweden, a cornerstone in optimizing surgical safety on the organizational level.

5.3.5 Importance of surgical volumes on the hospital level

In PAPER II – CASE VOLUME, the main finding was that operative volumes had an impact on operating time and outcomes in elective and acute cholecystectomy. High-volume hospitals had shorter operating times and fewer open surgeries in both elective and acute cholecystectomies, and a significantly lower 30-day mortality in acute surgery. Hospital volumes are difficult to interpret. Small units with low volumes might have a few high-volume surgeons while bigger hospitals with high volumes may have many low-volume surgeons. It has previously been suggested that hospital volume is less important than the individual surgeon's volume in technique-demanding procedures with short hospital stays, compared to procedures with a major need for perioperative

and intensive care, such as malignant procedures [143, 227]. More than 14,000 cholecystectomies are performed every year in Sweden. If all cholecystectomies were equally distributed, fewer than 200 procedures would be performed at each centre annually. No centre would be a high-volume hospital according to our definition of high-volume as >211 cholecystectomies/hospital/year. But case distribution is not equal and there is room for improvement. High-volume hospitals today are often regional or county hospitals or, in bigger cities, university hospitals with broader profiles or private clinics, which represent the opposite direction of centralization of malignant or rare conditions to high-volume centres. Some studies show that gallstone surgery varies between different regions in Sweden, which emphasizes the need for national recommendations [228, 229]. Centralization of gallstone surgery is not an easy solution for improving surgical safety.

5.3.6 Organization of high-volume centres in cholecystectomy

Previous studies on more complex surgeries have shown that volume is not the only explanation behind more favourable outcomes [144]. Multidisciplinary teams with high-volume surgeons available around the clock, well-established routines, standardized treatments, and standardized perioperative care are important in improving surgical safety and outcomes. This is also important for less complicated procedures. Hospitals with a high volume of gallstone surgery are more likely to have an organizational structure that is used to the procedure. Factors for surgical safety and high-quality care in gallstone surgery might include: an organization that promotes fast scheduling of surgery for patients with acute cholecystitis; surgeons with high annual volumes of cholecystectomies available around the clock; an efficient day surgery facility; competence in perioperative removal of gallstones; a high percentage of laparoscopically performed procedures; the capacity to handle surgical complications, and the use of GallRiks for quality control in clinical practice. Some of these important qualities were also highlighted in the recently published Swedish National Guidelines for Gallstone surgery [10].

5.4 DISCUSSION OF SURGICAL SAFETY ON THE INDIVIDUAL LEVEL

5.4.1 Importance of surgical volumes on the individual level

PAPER II - CASE VOLUME demonstrated that the surgeon's annual volume impacts surgical outcomes and operating time in elective and acute cholecystectomies. This finding is important when considering surgical safety on the individual level. The results are in line with previously published studies that found an association between high-volume surgeons and fewer complications in high-risk patients and acute cholecystitis [151, 152]. Our study is one of few that demonstrate better outcomes for surgeons and hospitals in both elective and acute surgery. Among our most interesting findings is the increased risk for surgical complications and bile duct injuries in elective surgery. Intraoperative complications reflect what is happening in the operating room, indicating that the surgeon's technical skill, knowledge of anatomy and decision-making might to some extent explain differences in outcomes.

5.4.2 The definition of high and low volumes

The volume-based associations on the surgical level are seen especially in elective surgery. In acute surgery, patient characteristics and the level of cholecystitis might have a greater impact on outcomes than the surgeon's case volume [230, 231]. In our study, we set a cut-off for low and high volume between quartile 2 and 3, defining low volume on the individual level as fewer than 20 cholecystectomies/year. Previous studies on case volume use different cut-offs, rendering them difficult to compare [143]. Existing limits in cholecystectomies vary from <10-37 for low volume surgeons and >13-40 for high volume surgeons [148, 149, 151, 152, 230-234]. In our study, less than 50% of the surgeons and hospitals performed more than 20 cholecystectomies/year.

5.4.3 The challenges of gallstone surgery

One of the major challenges with gallstone surgery is its variability. Acute cholecystectomies have a higher complication rate than elective procedures [39]. However, we can rarely foresee the level of difficulty. Elective surgery for uncomplicated biliary colic, in patients without complicating factors, might be an easy procedure with well-defined tissue layers (sometimes you hear the ironic nickname "consultant surgeon's cholecystectomy" or "överläkargalla" in Swedish). But elective surgeries can be extremely complicated, especially in cases of chronic cholecystitis where fibrosis might render the anatomy unrecognizable. This was illustrated in PAPER IV, when 31.5% of the elective procedures had an acute or chronic cholecystitis of the backwall. It is not rare for acute gallstone surgery to be performed out of hours by a consultant surgeon. These surgeons may have varying areas of interest (like breast surgery, colorectal surgery, trauma surgery etc.) and sometimes have limited volumes of laparoscopy and gallstone surgery in daytime practice. This might explain the higher conversion rates for low-volume surgeons in acute surgery. On the other hand, elective surgeries are often performed by surgeons in training, or procedure-dedicated surgeons. Interestingly, it is in elective surgery that we found an association between volume, surgical complications, and bile duct injury. In acute surgery it is probable that the level of the inflammation impact outcomes in a greater extent. Previously published studies suggest

that patients characteristics and the severity grade of an inflammation in acute surgery have a greater impact on outcomes than the surgeon volume [233] [230] [231].

5.4.4 Should gallstone surgery be performed by all surgeons?

Together with open hernia surgery and smaller surgeries (*chirurgia minor*), laparoscopic cholecystectomies are procedures that all surgical residents in Sweden are expected to perform independently after 5 years of training. It is also one of few procedures to be performed by most surgeons, like appendicitis, at least during one period of their career. The latest Tokyo Guidelines and SAGEs recommend that moderate to severe cholecystitis are performed at centres with high competence in gallstone surgery [31, 44, 69]. As previously mentioned, centralization of gallstone surgery is not an easy solution in a country like Sweden. However, in larger facilities with many surgeons, having a limited number of surgeons performing gallstone surgery could be discussed. Performing both elective and acute cholecystectomies is another way to maintain high volumes. This is an issue today, since elective surgeries in some cities are performed at private units, and some hospitals only do acute cholecystectomies [160]. Our study's important finding that high volume surgeons have more favourable outcomes emphasizes the importance of an accessible high-volume surgeon, available to operate on complicated cholecystectomies and to assist and advise less experienced surgeons in unexpectedly difficult cases.

5.4.5 Gender equity in surgical safety

In PAPER III – GENDER IN SURGERY, we introduced the aspect of gender differences in surgery. The paper's main finding is that female surgeons operate more slowly than male surgeons and have more favourable outcomes in both elective and acute gallstone surgery. The additional analysis presented in this thesis demonstrates that varying operating volumes alone cannot explain these differences. Our study differs from previously published studies because we studied one specific operation [166, 168, 169]. This made it possible to compare operating times as well as outcomes. Gender differences in medicine is still a surprisingly controversial topic. During the process of writing PAPER III, I have experienced different reactions, interesting comments, and varying interpretations. PAPER III was published in JAMA surgery together with an article by Wallis et al. on the same topic [235]. They analysed a Canadian cohort of more than one million patients, undergoing one of 25 different surgical procedures between 2007 and 2019. They found that patients treated by female surgeons were less likely to be readmitted to hospital, die, or have a major medical complication at 90 days or 1 year after surgery. The two papers strengthen each other and have been vividly discussed in different news media and forums after their publication. Interestingly, even after comments like "fake news" and negative comments about female surgeons, there are many references to research and reflections about surgical attitudes, and the need for a change. The article's first citation was in the British Medical Journal (BMJ) where the President of England's Royal College of Surgeons apologizes for "gaslighting" female surgeons in a news media comment on the articles [236]. Hopefully this debate might result in an awareness of remaining inequities.

5.4.6 Possible explanations for gender differences in surgery

Previous studies on gender differences in medicine have demonstrated that male and female physicians differ in practice style. Female physicians have been found to use a more patient-centred communication style and to be more collaborative and careful about patient selection [237-239]. These qualities are, of course, found in both female and male physicians. In the Canadian study, the significance in outcomes was especially prominent for elective surgeries, and the authors discuss whether preoperative care processes and surgical selection might explain some of their results [235]. Our study demonstrated that for male surgeons in elective and acute operations, there was an increased risk of surgical complications: a composite of major bleeding, visceral injury, bile duct injury, bile leakage and abscesses. In addition, the total complication rate was slightly higher in patients treated by male surgeons. Previous studies have suggested that technical ability may be associated with short term surgical outcomes, and factors like patient selection may contribute to long term outcomes [240].

GallRiks does not contain information about years in practice and a surgeon's characteristics such as personal qualities and attitudes, which would have helped in understanding the rationale behind the results. However, intraoperative complications occur in the operating room. It is therefore likely that differences in surgical technique, attitudes, teamwork, decision making and risk-taking behaviour might each play a role. This is a field for future research. Another explanation is that the association between the surgeon's gender and patient outcomes might not be equally distributed between male and female surgeons, or within the operating team. Wallis et al. have analysed the same cohort in two previous publications on sex discrepancy. In the first study, female patients treated by male surgeons had worse outcomes compared to female patients treated by female surgeons [241]. The second study showed that patients operated on by surgeon-anaesthesiologist teams with only male physicians had longer hospital stays and the highest postoperative mortality [242, 243]. In a study on stereotypes in surgery, the public graded surgeons as high in warmth and competence, compared to other physicians [244]. When comparing female to male surgeons, female surgeons received high warmth grades, but lower competence ratings, compared to male surgeons. This contradicts a study on medical students' and nurses' perceptions of surgeons, in which they describe surgeons as competitive, egoistic, aggressive, domineering, and stubborn, but also technically masterful, precise, and energetic [244]. The patient's impressions of the surgeon play a role in patient satisfaction, and adherence to rehabilitation programs. Female surgeons' more patient-centred communication may result in better patient compliance for smoking and alcohol avoidance before and after surgery and thus promote more successful rehabilitation [235].

5.4.7 The significance of gender-based research in surgery

In a global perspective, there are countries where the general belief is that male surgeons are better than female surgeons [163]. However, most previously published studies indicate that female surgeons are at least equal to men, or even slightly better, as seen in our study [166, 169, 245]. Based on the magnitude of the reactions to our studies, more gender-based medical research is needed. Recruitment of more women as surgical specialists can be one way to increase the workforce in countries that lack surgeons [163]. Our study within the Swedish population highlights inequities within the

surgical workforce. Female surgeons had significantly lower annual volumes, worked somewhat more often at universities and private clinics and did slightly more elective procedures. We do not know why these differences exist but part-time work, inequities in the hospital's organization, fewer night shifts and longer parental leaves are possible explanations. The proportion of female surgeons slowly increased during the study period, but female surgeons are still in the minority, unlike in many other medical specialties [163]. In the latest statistics from the Swedish National Board of Health and Welfare (2021), 32.6% of general surgeons were female [164]. The corresponding data for related subspecialities were 19% in vascular surgery, 18% in neurosurgery, 18% in thoracic surgery, 28% in plastic surgery and 20% in orthopaedic surgery. In addition, female surgeons are less represented in academia and leading positions worldwide [165, 246, 247]. As an illustrative example, Malin Sund became Sweden's first female Professor of Surgery as late as in 2013 [248]. Promoting gender equity is of great importance for a balanced workforce. If female surgeons have slightly better outcomes, then gender equity also has an impact on surgical safety.

5.4.8 Implications for education and recruitment

Studies on medical students have found that experience from computer games and a general interest in the surgical specialty correlated with better acquisition of surgical skills, for both genders [249]. The same systematic review found that male medical students had better results in laparoscopic and virtual reality simulations, but these differences did not remain for residents. This indicates that female residents respond better to feedback and training and stresses the importance of caution in recruitment and motivation of potential residents [249]. If the selection of surgeons is based on early results, many candidates with high potential may be excluded. Recruitment profits from being potential-based, where qualities such as caution, accuracy and precision should be esteemed more highly, no matter what the applicant's gender. Most European countries use different recruitment processes [250]. In Sweden, the recruitment process is not regulated, and sometimes personal connections and preferences guide the choice of candidate, instead of formal competence. An evidence-based selection system has been suggested to avoid biased recruitment [250]. Research results acknowledging that female surgeons are equal to men, or even better, could be used to encourage young female physicians to choose a surgical specialty.

5.5 DISCUSSION OF SURGICAL SAFETY ON THE TECHNICAL LEVEL

5.5.1 The learning curve for ultrasonic fundus-first dissection

In PAPER IV – LEFFE, the main finding was that ultrasonic fundus-first dissection is easy to learn with a low complication rate during the first 15 operations, for both residents and specialists. Developing surgical techniques is a way to improve surgical safety and the study showed that ultrasonic dissection is an alternative to traditional electrocautery dissection. Above all, our study was a pilot study leading to PAPER V – SONOCHOL, to learn the technique and assure surgical safety. Our study adds to the existing literature of a heterogenous set of learning curve studies on laparoscopic cholecystectomies [251]. However, it stands out by focusing on only the fundus-first approach. We decided to include 15 operations per surgeon, based on their previous experience of gallstone surgery with electrocautery dissection. For residents we did not observe a flattened curve and it is possible than an increased number of operations would have yielded that. The heterogenous approaches of learning curve studies render them difficult to compare. We used operating time and complications as a measure of the learning curve, which has been used in several other studies [252-254]. Another approach, which has gained in popularity amongst surgical learning curve studies, is to illustrate learning curves with the cumulative sum procedure (CUSUM). This is a graphical method that illustrates learning curves based on surgical outcomes, or operating time, thus highlighting when the "plateau" is reached [255, 256]. A recently published study using the CUSUM approach determined that the learning phase of laparoscopic cholecystectomies was completed within 25 procedures (range 7 to 25 procedures) [257].

5.5.2 Why did we use ultrasonic fundus-first dissection?

The decision to study ultrasonic fundus-first dissection was based on the experiences of the surgical team in Sundsvall [190, 212]. For us, ultrasonic dissection was related to the fundus-first technique, and in PAPER IV it was never a question of starting the dissection from the cystic duct. The fundus-first technique has been criticized for increasing the risk of vascular and bile duct injuries, especially in cases with inflammation [195]. Most early studies analysed the fundus-first approach in general and not with ultrasonic dissection. This somewhat undeserved bad reputation remains. Nevertheless, fundus-first is well accepted as an alternative approach in complicated cases [31, 69, 71]. In fundus-first dissection, it is essential to find the right plane of dissection along the inner layer of the serosa of the gallbladder [258]. This might be difficult in cases of acute and chronic cholecystitis when the inflammation alters the normal histology. An extra safety measure in our study was to start the fundus-first dissection by marking the peritoneum where the cystic duct was estimated to enter the gallbladder. When the fundus-first dissection reached this mark, the surgeons new that it was time to stop. At the end of the study most surgeons still preferred to start the dissection from the triangle of Calot and continue upwards. It is possible that 15 operations per surgeon was not enough to really appreciate the potential of the technique. When designing the randomized controlled trial, we decided not to specify the direction of the dissection, and to let the surgeons choose the appropriate technique due to personal preference and anatomical conditions. This was based on our experiences from PAPER IV and a previous

randomized trial that concluded that the positive results with ultrasonic dissection in elective surgery were assumed to be associated with the instrument, and not the direction of the dissection [190]. In PAPER V, most surgeons used the instrument from the triangle of Calot and upwards.

5.5.3 Technical aspects of ultrasonic fundus-first dissection

A highlight, somewhat outside the primary endpoint of the learning-curve study, was the feed-back we received from the operating surgeons after the inclusion was completed. Some clinical experiences are listed in the article's discussion, but some reflections are worth mentioning here, since it is important for surgical safety on the technical level. The surgeons' overall opinion was that ultrasonic dissection is well suited for cholecystectomy. The instrument is especially useful in highly vascularized cases, due to its efficient vessel-sealing capacities. Other advantages are the instrument's efficacy in dividing adhesions and the walls of thick chronic gallbladders. It is timesaving that the same instrument can be used for most parts of the operation, including dividing the cystic artery. The instrument's design as scissors can be used in various ways. The compression in the instrument is useful for dividing tissue and adherences but the instrument can also be activated in the open position, using only the active blade. This is useful when opening the peritoneum and for stopping tiny bleedings. A closed instrument, without activation, can be used for blunt dissection. The hot active blade can cause thermal injuries and requires caution. It can be rapidly cooled down by holding it against a compress, or tissue. Its improved ergonomics is a great advantage since the instrument is activated in the hand, and not with a foot pedal like the older versions of electrocautery. However, some disadvantages were also mentioned, mostly related to the fundus-first dissection rather than the instrument. It might be difficulty to find the right plane for the fundus-first dissection in inflamed gallbladders, leading to perforations or damage to the liver capsule. This is less of a problem when you dissect from the triangle of Calot. Some surgeons felt uncertainty when dissecting towards dangerous structures, and not away from them. When the fundus-first dissection is finished, the surgeon has achieved the optimal critical view of safety because only two structures and an already dissected gallbladder remain. However, the gallbladder can twist, and it is difficult to insert a catheter in a twisted cystic duct. An active assistant is very important in fundus-first dissection because an appropriate counter tension is needed. This was illustrated in our paper since 50% of often apical gallbladder perforations occurred with an inexperienced assistant. The instrument used in PAPER IV was considered too blunt, which is why we decided to use the updated version with a slightly curved tip in PAPER V.

5.5.4 Ultrasonic dissection in acute cholecystitis

The main finding in PAPER V was that ultrasonic dissection has a total complication rate comparable to electrocautery dissection. However, in terms of advanced acute cholecystitis, fewer haemostatic products were needed, and surgeons tended to convert to ultrasonic dissection instead of open surgery. This demonstrates the importance of the instrument's qualities. Surgical safety in cholecystectomy includes optimization of the surgical technique and ultrasonic dissection is another tool to use, especially in advanced cholecystitis but also in chronic cholecystitis with thick

gallbladders. Our results are in line with a previously published single-centre study of 42 patients with acute cholecystitis that resulted in fewer conversions to open surgery and significantly lower blood loss in patients with ultrasonic dissection [259]. The authors also did a prospective evaluation of 101 patients before the RCT, that indicated the same results [260]. In addition, more intensive inflammatory response has been demonstrated with electrocautery compared to ultrasonic dissection, especially in patients with acute cholecystitis and biliary peritonitis [261]. One main argument against ultrasonic dissection is the increased instrument costs. However, previous studies in the elective setting have demonstrated decreased direct and indirect costs, from shorter operating times and hospital stays as well as shorter sick leaves [262, 263]. In our study, the finding that ultrasonic dissection decreased the use of haemostatic agents is important from a financial perspective.

5.6 STRENGTHS AND LIMITATIONS

PAPERS I-III – POPULATION-BASED COHORT STUDIES

Strengths

Sweden's national health registries are internationally unique, and are a valuable source for quality control and research [204]. Well-functioning registries can complement randomized clinical trials (RCTs). The large cohorts can be used to study rare conditions which would not be possible or realistic within an RCT. Although the importance of RCTs in evidence-based medicine is indisputable, insufficient statistical power, time, and costs limit their value. GallRiks has a role in all papers included in this thesis. PAPERS I-III are registry-based studies and in PAPERS IV and V data from GallRiks complement the CRFs. GallRiks is a widely recognized registry and the national coverage of 94.6% and the 97% follow-up are important strengths of both the registry and included papers [39]. The database includes the majority of the country's cholecystectomies since 2005, and more than 200,000 cholecystectomies are available for quality assessment and research [39]. The validity of the data is checked regularly by independent reviewers and a previous validation study found no failure to report serious adverse events [206].

Limitations

There are several limitations with registry-based cohort studies. Despite the high national coverage of 94.6%, information on 5.4% of the operations are missing. In the 2022 annual GallRiks report, eleven centres had coverage of less than 90% and nine of these were high-volume hospitals [39]. The importance of correctly entered data is the cornerstone of high-quality registers. In 2018, we published a study on the completeness of the 30-day follow-up in GallRiks, in relation to intra- and postoperative outcomes (not included in this thesis) [264]. The study demonstrated that centres with a high follow-up frequency had more postoperative adverse events, whereas centres with a low follow-up frequency had fewer postoperative adverse events, indicating the possibility that information on complications is missing. We suggested that a high follow-up frequency might serve as an additional quality indicator for health registries.

A registry changes over time. New variables are introduced, others are removed, and some are not compulsory. One example of a non-compulsory variable is BMI which is missing from records of 40% of the procedures. BMI is a known risk factor for more complicated gallstone surgery and the incomplete data is a limitation. When discussing registry-based research, you sometimes hear expressions like "garbage in, garbage out". We still can assume that most of what is registered in a high-quality registry is correct and that the huge cohorts compensate for some imbalances in data. However, until we know that the national coverage and follow-up frequency are 100% and that all data are correctly registered, the results from register-based cohort studies must be interpreted with some caution.

PAPER IV – CLINICAL OBSERVATIONAL STUDY

Strengths

The study's design as a multicentre study with surgeons from community hospitals, regional hospitals, and university clinics, in different parts of Sweden, are strengths of the study. We included both residents and specialists and their experience of gallstone surgery was equally distributed. The dataset was nearly complete with only a limited amount of missing data. The surgeons' operating techniques were graded and assessed by external surgeons in the video recordings, in addition to assessment of operating time and complication rates. The varying methods used for learning curve assessment are also a strength of the study.

Limitations

An observational study based on many subjective assessments has several limitations. The video-assessors' engagement in terms of time as well as personal technique and preferences certainly affects their grading. To compensate for this, we used two independent assessors. Their correlation coefficient was high for the most objective error definition "gallbladder perforation", and significant for "lack of progress" and "incorrect plane of dissection". No significant correlation was demonstrated for the more subjective definitions. Another limitation is that we did not define the time interval between the first and fifteenth operations beforehand, for practical reasons. The varying time intervals were due to parental leave, reorganization of elective and acute surgery and lack of equipment. In retrospect, it is likely that a time frame that we had limited beforehand would have resulted in many drop-outs and incomplete inclusion.

PAPER V – RANDOMIZED CONTROLLED TRIAL

Strengths

The study's design as a randomized double-blind, parallel-group, controlled trial performed at eight different hospitals in Sweden, including university clinics, regional hospitals, and county hospitals, is a strength of the study. Well-designed RCTs are the fundaments of clinically based medicine [265]. This study included 300 acute cholecystectomies, which is a relatively high number for a surgical RCT [265]. It is also more

complicated to perform a study on acute operations, which we managed to do within a reasonable time limit.

Limitations

Despite the design as an RCT, this study has its limitations. Since only surgeons with previous experience of both techniques could operate, a lot of eligible patients were not considered for inclusion in the study. Only surgeons that had participated in PAPER IV or who could demonstrate that they had mastered the technique in video assessment, were invited to participate. However, most surgeons had more experience of electrocautery dissection, and it is possible that the learning curve for ultrasonic dissection had not reached its plateau. This might underestimate the effect of ultrasonic dissection. Despite the randomization, the intervention group included more males and the patients had higher ASA scores. This allocation occurred by chance but, since all these differences are associated with a higher risk for complications, it could lead to underestimation of the treatment effect of ultrasonic dissection. We based our information about adverse events on registry data and verified and complemented this with patient-reported outcomes from the study's 30-day follow-up. An additional twelve postoperative complications were found during this process, indicating missing data in the registry. We decided to include all registered complications. However, it is unlikely that complications like urinary retention and urinary infection are related to the instrument that was allocated. A pre-set cut off for Clavien-Dindo 2 or higher, could have been more appropriate approach.

5.7 METHODOLOGICAL CONSIDERATIONS

Some methodological considerations will be discussed briefly, based on the included papers. I will finish with some reflections about surgical RCTs and my experiences from conducting multicentre trials.

Validity

Internal validity refers to a causal association between the exposure and the outcome, i.e., whether we can be sure that the outcome is caused by the exposure. However, systematic errors (i.e., bias) might impact internal validity and can result in inaccuracy which distorts the results and obscures the actual association. Systematic errors refer to faults in the study design, as opposed to random errors which occur by chance (and can decrease with increasing study populations). Selection bias, misclassification bias, and confounding are systematic errors that might lead to underestimation or overestimation of the results. These factors must be considered when planning, conducting, and compiling medical research. A well-designed RCT has high internal validity, and mostly an acceptable external validity (or generalizability) [266]. Randomization balances known and unknown confounding factors, which must be identified and included in the analysis in a more active way in observational studies. Systematic errors in RCTs can be minimized by using randomization, concealment of allocation, blinding, complete follow-up and intention-to-treat analysis [266]. Random errors are minimized by a realistic power calculation. High quality data, complete follow-

up, realistic power calculations, proper choice of statistical analysis and a careful consideration and inclusion of possible confounders are all essential in observational studies. Directed Acyclic Graphs (DAGs) are a useful tool used to visualize the possible pathways and relationships between exposure, outcome, confounders and mediators [267]. In PAPER V, the internal validity cannot be disputed to any great degree. We used an intraoperative randomization, which results in concealment of the allocated treatment. In addition, patients, postoperative caregivers, and follow-up personnel were blinded to the allocation and we did the analysis according to the intention-to-treat principle. However, in retrospect, the power calculation for the primary outcome was too optimistic. In addition, we cannot rule out the fact that ultrasonic dissection in the hands of more experienced surgeons, far beyond the learning curve, would have somewhat lower complication rates. In statistical terms, it means that a type II error might exist (false negative results). In the observational studies, PAPERS I-IV, internal validity is relatively high due to the huge cohorts (and complete registrations in PAPER IV), but systematic errors might exist, as discussed below.

Bias

Selection bias can occur if participation in a study is related to both exposure and outcome. It can also occur if patients drop out or if there is loss to follow-up. In PAPERS I-III, selection bias could have been introduced if the surgeon avoided reporting on negative adverse events and if follow-up was incomplete in selected patients. The randomization and concealment of allocation in the RCT was an efficient way of handling selection bias.

Misclassification bias

Misclassification can occur when the information about the study participants or outcomes are incorrect. It can be either an exposure or outcome misclassification. In registry-based studies, misclassification can be introduced with wrongly assessed exposures or incorrect outcomes. In PAPERS I-III, incorrect information about timing, volumes or gender might result in exposure misclassification. In PAPER II, exposure misclassification of some surgeon's annual volumes is probable. The registry does not include information about experience and years in practice, and we based our calculations on the number of procedures performed the year before each procedure under study. Experienced surgeons might be wrongly classified as low-volume surgeons if they mainly assist younger surgeons. In addition, inexperienced surgeons might be high-volume surgeons early in their career due to short rotations in gallstone surgery at private clinics. This non-differential misclassification might underestimate the results.

The definition of a cohort study is that exposure is registered before the outcome has occurred. In theory, this is the case for register-based studies. Data should be registered immediately after surgery to reduce the risk of differential exposure, or outcome misclassification (i.e., recall bias). In some units, the operation is registered online, during and immediately after surgery. However, this routine is not implemented everywhere, and registry data might be entered in retrospect (sometimes before the annual report is written several months later). The 30-day follow-up report is based on medical records, and Sweden's various regions and some hospitals, such as private clinics, use different

digital systems. Therefore, complications managed at hospitals other than the primary hospital, or abroad, might not be registered. In addition, medical complications might be missed if the coordinator only has access to the medical records within the surgical department. To assess this, GallRiks includes a variable in the 30-day follow-up where the coordinators register how the complications are diagnosed. Incomplete follow-up might lead to a direct outcome misclassification which might both over- and underestimate the results. One way to handle this is to include only complete cases in the analysis.

Confounding

Confounding is another important challenge in population-based cohort studies and must be carefully considered. The definition of a confounder is a factor that is associated with both the exposure and the outcome, and that it is not an effect of the exposure (i.e., not a mediator). We have aimed to identify and include the possible confounders in PAPERS I-III. However, it might sometimes be difficult due to limitations in the registry, like the incomplete BMI variable. It is also a challenge to include a reasonable number of confounders. From experience, this is also a matter of subjective assessment and the impact of peer-review of submitted manuscripts. Despite a careful assessment of possible confounders, we cannot fully rule out that residual confounding may exist. Participating individuals might also share certain characteristics, and the risk of case mix is another weakness with population-based studies.

Surgical Randomized Controlled Trials

Reliable, high-quality RCTs require a high level of methodological quality [265]. Over the years, surgical RCTs have been sparce and are widely considered to be of low quality [266, 268, 269]. Many innovations are introduced outside of study protocols without regulated evaluations, since studies regarding surgical procedures are considered too challenging to perform. In 2009, the IDEAL recommendations were introduced with a five-stage description of the development of new surgical techniques (Idea (1), Development (2a), Exploration (2b), Assessment (3) and Long-term study (4)) [268, 269]. According to these recommendations, PAPER IV is a stage 2b trial and PAPER V possibly a stage 3 trial.

Surgical studies face challenges that are less prominent in other medical trials [265, 266, 270]. Some examples are:

- *Surgeon-volume:* When comparing the effect of an established surgical method with a new technique, there is a risk of biased results. This was the case in our study, since many surgeons had more experience with electrocautery. This might lead to better outcomes for electrocautery because the surgeon is more comfortable with the procedure and not because of the procedure itself. Surgeon experience might also impact results if low and high-volume surgeons are included in the same trial.
- *Timing:* If the study is done too early, the results may reflect a stage of development and learning rather than the effect of the instrument.
- *Personal preferences:* In some cases there might be poor compliance with using the allocated instrument due to personal preferences. We had cross-over in

both directions in our study. Personal preferences may also complicate inclusion if either the surgeon or the patient prefers one technique over the other.

- *Teamwork:* Surgery is teamwork, both around the operating table and in the operating room. The level of experience of the team may also influence results.
- *Standardized classifications:* Surgical RCTs often use different endpoints, sometimes chosen by the surgeons themselves. If outcomes are not standardized, results are not reproducible. A way to overcome this is to use a classification system, such as the Clavien-Dindo system for complications.
- *Surgeon gender:* When I presented PAPER III at a conference, the question came up: "Will you adjust for the surgeon's gender in all upcoming trials?". The answer is probably not, but it is a good question worthy of further exploration.
- *Patient perspective:* The patient's perspective might be different from the surgeon's perspective and it is important to include patient-reported outcomes.

Most of these challenges are complex and difficult to overcome. If the study is too structured and homogenous, its external validity/generalizability will be affected. Perfect is not possible. The best option might be to conduct a study in a realistic setting. I think these words summarize what is essential: "The key questions to address when planning a study of a surgical intervention are: what is the outcome, how should it be measured, who should assess it, and when?" [270]. And "When designing a surgical trial, the choice and selection of outcome measure should be based on what is important to the patient" [266].

5.8 MY EXPERIENCES FROM CONDUCTING MULTICENTRE STUDIES

This thesis includes two clinical multicentre studies. PAPER IV was conducted between 2017 and 2019 and PAPER V between 2019 and 2023, somewhat delayed by the pandemic during 2020-2021. It has been both rewarding and challenging to organize these studies and I will finish with some personal experiences and reflections.

In PAPER IV, the major challenges were organizational issues with reorganization of elective and acute surgery, lack of resources for ultrasonic dissection and varying opportunities for video recordings. In PAPER V, the main challenges were on the individual level since inclusion was limited by the availability of a participating surgeon. Patients with acute cholecystitis often undergo surgery out of hours, or by the on-call surgeon, and many eligible patients were not included. In complicated cases, surgeons tend to prefer their traditional technique, which might have an impact on inclusion. Although by tradition, most research studies are conducted at university clinics, it is possible to organize and conduct multicentre studies beyond the university. In clinics where research is not integrated into daily work, it is crucial to include the support of the department director, helpful colleagues and (if possible) a dedicated research nurse. I have had the privilege of outstanding support and help with the clinical studies in this thesis.

A general reflection is that conducting multicentre studies requires patience because it takes time. In addition, it can serve as a crash course in surgeon psychology. We are all different, with strong opinions, and varying levels of engagement are not uncommon. I also recognize that it is essential to have an answer to the question, "What is in it for me?" Some kind of incentive is needed for faster progression. Luckily, learning a new technique is motivating for most surgeons. During the planning of PAPER V, we

discussed additional laboratory analyses and histopathological examination of all gallbladders, but we decided to keep it simple. In addition, we adopted a very user-friendly module for randomization and a simple e-CRF, which could be completed online in the operating room. Complicated modules might limit inclusion. We used GallRiks to collect data about patient characteristics, operation-specific variables, and complications. The aim was to save time for the participating surgeons. The idea was sound until the dataset was received, and I realised that some data were missing. The 30-day follow-up was also incomplete and had to be complemented afterwards, delaying the analysis.

Conducting clinical trials is taught in courses like Good Clinical Practice. I have taken the course, but also learnt it the hard way. If someone were to ask me for advice before starting a multicentre surgical trial, I would recommend the following:

- Make sure of support from the department director and motivate your collegues and team before the start of the study.
- Get a collaborator and/or a local representative at each hospital, to motivate participants, facilitate inclusion and aid in completing missing data.
- Choose a user-friendly module for randomization and an easy e-CRF.
- Keep it simple.
- Consider the variables carefully and try to avoid getting a dataset with more than 700 variables.
- Establish a contact with a statistician early and create a detailed analysis plan.
- Write the application for ethics approval when the protocol is finished.
- Carefully consider your primary endpoint and the power analysis.
- Use a reliable information source. GallRiks is useful but make sure that participants register the information needed.
- Offer an answer to the question “What is in it for me?”.
- Work on the team spirit. If possible do something social together.
- Frequent updates to all participating surgeons and collegues are highly appreciated.

CONCLUSIONS

The five papers in this thesis highlight different aspect of surgical safety in gallstone surgery. The conclusions are:

ORGANIZATIONAL LEVEL

- The optimal timing of cholecystectomy for patients with acute cholecystits is within two days of hospital admission.

- Hospital volume matters in cholecystectomies. Patients with gallstone-related diseases profit from undergoing surgery at hospitals with large annual volumes of cholecystectomies.

INDIVIDUAL LEVEL

- Surgeon volume matters in cholecystectomies. Patients with gallstone-related diseases profit from being operated on by dedicated surgeons with large annual volumes of cholecystectomies.

- Female surgeons operate more slowly but have more favourable outcomes in elective and acute gallstone surgery.

- Ultrasonic fundus-first dissection in elective gallstone surgery is easy to learn, for both residents and specialists.

TECHNICAL LEVEL

- Ultrasonic fundus-first dissection can be considered safe in elective cholecystectomies for surgeons with no previous experience with the technique.

- Ultrasonic dissection can be used as an alternative to electrocautery dissection in patients with acute cholecytitis, or as a complement in complicated cases.

POINTS OF PERSPECTIVE

My work towards this thesis has been a great introduction to the field of medical research. The papers' various designs and perspectives have taught me to organize and conduct different kinds of studies. It has also demonstrated the need for further knowledge and research within the field.

GallRiks is an excellent source of data for future projects. I have spent many hours organizing and analysing datasets from GallRiks, and this has generated several ideas for future projects. A well-established study design, not yet adapted to GallRiks, is the Registry-based Randomized Controlled Trial (RRCT) [271]. In an RRCT, randomization is integrated into the registry and many patients can be included, at costs lower than traditional RCTs. However, this function is not yet integrated in GallRiks, due to financial and organizational issues. I think this is important and crucial for the registry's future. However, it is very important to continue working with the standardization of the 30-day follow-up. An RRCT with incomplete follow-up is not ideal. In a futuristic vision, registries are integrated into the medical record system, increasing standardization, and decreasing the need for an individual coordinator at each unit.

On the **organizational level,** I hope that the national and global problems of health care today, including lack of resources, will improve in the future. However, this positive vision seems somewhat unrealistic. On a smaller scale, we can at least wish for better organizational structures and resources for acute surgery for patients with acute cholecystitis. In my futuristic vision, video-recordings are just as evident as the use of a black-box in the airline industry.

On the **individual level,** I wish for equal gender distribution in the surgical specialty. It will be very interesting to continue the work begun in PAPER III and study possible explanations for demonstrated gender differences. Many challenges await the education of future surgeons, including maintaining competence, both in laparoscopic/robotic surgery and open surgery. The need for competence in open surgery has become relevant again due to the changing safety in the world with political situations, natural disasters, and wars. Development of advanced simulation for both open and laparoscopic surgery is important in training.

In the **patient perspective,** the high levels of postoperative pain and functional disorders stresses the importance of research on surgical indications in elective surgery. To predict surgical difficulty and mortality in patients with acute cholecystitis, a scoring system, equivalent to the OS-MRS in obesity surgery, might be useful [272, 273]. For cholecystectomies, it may include male gender, BMI, age >70, and previous cholecystitis.

On the **technical level,** it will be interesting to follow the development of different surgical instruments. An ultrasonic device with shorter blades and even higher precision could be useful in cholecystectomy. Robotic surgery is here to stay, and with decreasing costs and increasing access, it is likely that it will also be used in less complex procedures. Another field of interest is artificial intelligence (AI). In gallstone surgery, AI might aid in identification of dangerous zones when dissecting anatomical landmarks, like the CVS and even cholangiographies. Research is ongoing and some publications demonstrate promising results [274, 275].

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THE HISTORY OF FEMALE SURGEONS

When studying the literature, three periods can be distinguished. In this thesis they will be named as "the long surprisingly acceptable time", "the bad time" and "the short promising recent time".

The long surprisingly acceptable time

As early as 3,500 BC, there are signs of female surgeons. Surgical instruments of flint and bronze were found in the tomb of Queen Shubad of Ur. In 1,500 BC, female medical students were registered in Heliopolis in Egypt. Female surgeons and doctors are mentioned in the Bible and Talmud, and in Greek mythology Leto, the lover of Zeus and mother to Apollon, is known to have performed surgery and cure nasty wounds. Asclepius, the god of medicine had four daughters known to have been practicing medicine. The medical abilities of Greek prisoners were highly esteemed and paid for when sold to Italy. A Greco-Roman gynaecologist/surgeon, Aspasia, was teacher to Aetius who wrote Tetrabiblion, a well-known gynaecologic work [276, 277].

The bad times

The male-dominated Christian church considered females lower in value and prohibited them from practicing medicine and surgery. The Middle Ages, from 500 AD to the 15th century, was not good for the medical sciences and especially bad for female surgeons. Female surgeons could continue to study medicine for some time in Italy, at the Salerno medical school, the first medical university. The well-known 12th century book, the Trotula, had three parts:" Conditions of women"," Treatments for women" and" Women's Cosmetics". The second part was written by a female doctor and gynaecologist, Trota of Salerno. In 1313, female surgeons could only practice medicine if they were judged by a competent jury. Henry VIII said that "no carpenter, smith, weaver or women shall practice surgery" but for a few centuries it was possible if a woman inherited her late husband's practice. Despite this, female physicians and surgeons continued to practice medicine without recognition [276, 277].

The present times

In 1812, a surgeon named James Barry (1795-1865) finished Edinburgh Medical School and worked actively within the British army. When he died, the autopsy showed that he was in fact a woman, born Miranda Steward. The first modern female doctor is Elisabeth Blackwell (1821-1910) who graduated from Geneva Medical College in 1849. She also had an interest in surgery and is sometimes mentioned as the first female surgeon. Mary Edwards Walker (1832-1919) graduated from Syracuse Medical College in New York in 1855 and in 1863 was the first female surgeon in the army. The first female doctor in Sweden was Karolina Widerström (1856-1949) who graduated from Karolinska Institutet in 1884 and opened her own clinic in 1893, where operations were possible. The first woman Swedish to be mentioned as surgeon was Gertrud Gussander (1872-1950) who became medical doctor in Lund in 1912. Sweden appointed its first female professor in surgery in 2013, Malin Sund [248].

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