Department of Gastrointestinal Surgery, Abdominal Centre
Helsinki University Hospital

Doctoral Programme in Clinical Research
University of Helsinki

LAPAROSCOPIC CHOLECYSTECTOMY FOR CHOLECYSTITIS AND GALLSTONE DISEASE:

RISK FACTORS FOR ADVERSE OUTCOMES, AND THE ROLE OF THE SURGEON AND SURGICAL TECHNIQUE

Petra Terho

DOCTORAL DISSERTATION

To be presented,
with the permission of the Faculty of Medicine of the University of Helsinki,
for public examination, in Lecture Hall 1, Haartman Institute
on the 21st of October 2022 at 12 o'clock.

Helsinki 2022

Supervisors
Adjunct professor Panu Mentula MD, PhD
Department of Gastrointestinal Surgery
Helsinki University Hospital
Helsinki, Finland

Adjunct professor Ville Sallinen MD, PhD
Department of Liver and Transplantation Surgery
Department of Gastrointestinal Surgery
Helsinki University Hospital
Helsinki, Finland

Reviewers
Adjunct professor Jukka Karvonen MD, PhD
Department of Gastrointestinal Surgery
Turku University Hospital
Turku, Finland

Professor Joonas Kauppila MD, PhD
Department of Surgery
Oulu University Hospital
Department of Clinical Epidemiology
University of Oulu
Oulu, Finland

Opponent
Professor Ewen Harrison, MB ChB, PhD
Centre for Medical Informatics
University of Edinburgh
Hepatobiliary and Pancreatic Unit
Royal Infirmary of Edinburgh
Edinburgh, UK

Illustrations created with Biorender.com

Unigrafia
Helsinki 2022

ISBN 978-951-51-8560-0 (paperback)
ISBN 978-951-51-8561-7 (PDF)

The Faculty of Medicine uses the Urkund system (plagiarism recognition) to examine all doctoral dissertations.

To my family

TABLE OF CONTENTS

ABSTRACT

Background Laparoscopic cholecystectomy (LCC) is among the most common abdominal operations – 9000 LCCs are annually performed in Finland. However, associated conversion, bile duct injuries (BDIs) and postoperative complications all lower patients' quality of life. Knowledge of risk factors for complications, sufficient cumulative and annual experience, and safe bile duct identification techniques such as the Critical View of Safety (CVS) could all help raise the standard of care.

Aims First, this thesis aimed at investigating risk factors for conversion and postoperative complications in LCC for acute calculous cholecystitis. Second, it aimed at investigating how surgeons' experience and annual caseloads are associated with conversion, postoperative complications, and operating time in LCC for acute cholecystitis. Third, it aimed at examining the association of correct use of CVS with BDIs and postoperative complications, and fourth, at estimating the use of CVS among individual surgeons.

Methods All studies took place at Helsinki University Hospital. Study I retrospectively analysed 373 patients treated for acute cholecystitis in 2013-2014. Multivariate logistic regression identified risk factors for conversion and postoperative complications. Study II retrospectively analyzed 892 patients treated for acute cholecystitis in 2013-2016. Surgeons were compared regarding annual volume (>5 LCCs for acute cholecystitis/year *vs.* ≤ 5 LCCs/year) and experience (consultants *vs.* residents). In Study III & IV, surgeons photographed the view before clipping the cystic duct and artery in LCCs in 2018-2019. A lecture on safe LCC was given halfway through the study. Independent raters scored photos for satisfactory CVS. Study III evaluated the association of satisfactory CVS with BDIs and postoperative complications. Study IV compared rates of satisfactory CVS, BDIs and postoperative complications among residents and consultants. Study IV also evaluated the effect of the intervention lecture on the rates of photographed procedures and satisfactory CVS.

Results In Study I, 84 (22.5%) of 373 patients had conversion to open surgery. Multivariate logistic regression identified C-reactive protein (CRP) over 150 mg/l, age over 65 years, diabetes, gangrene of the gallbladder and abscess as risk factors for conversion. Altogether, 67 (18.0%) patients had postoperative complications. Multivariate logistic regression identified age over 65 years, male sex, impaired renal function, and conversion as risk factors for postoperative complications. In Study II, high-volume surgeons operated faster than low-volume surgeons (91 min *vs.* 108 min, p. <0.001). Examining consultants only, high-volume consultants converted less (14.9% *vs.* 32.0%, p<0.001) and operated faster (95 min *vs.* 110 min, p<0.001) compared with low-volume consultants. In Study III, of 1532 patients, CVS was satisfactory in 354 (23.1%), unsatisfactory in 823 (53.7%), and photos were missing in 355 (23.2%) patients. Patients with satisfactory CVS had the lowest BDI rate compared with unsatisfactory CVS or missing photos (0.3% *vs.* 1.0% *vs.* 2.3%, p=0.012). Patients with satisfactory CVS had the lowest postoperative

complication rate compared with patients with unsatisfactory CVS or without photos (4.8% *vs.* 7.9 *vs.* 9.9%, p=0.011). In Study IV, residents had higher rates of satisfactory CVS in elective LCCs compared with consultants (34.9% *vs.* 23.0%, p<0.001), but not in emergency LCCs (18.4% *vs.* 15.0%, p = 0.252). No significant differences in BDIs or postoperative complications emerged between residents and consultants. After the lecture, the rate of photographed elective LCCs rose from 74.0% to 80.3%, p=0.032, but the rate of photographed emergency LCCs did not change significantly. The rates of satisfactory CVS, BDIs or postoperative complications after the lecture did not significantly differ from those before the lecture.

Conclusions Advanced cholecystitis with high CRP, gangrene or abscess raises the risk of conversion. Conversion raises the risk of postoperative complications. Consultants performing > 5 LCCs for acute cholecystitis a year have shorter operative times and lower conversion rates. Centralising LCC for acute cholecystitis to fewer consultants could improve outcomes. Intraoperative photo documentation of satisfactory CVS is associated with lower rates of BDIs and postoperative complications. To raise rates of satisfactory CVS, stronger interventions than single lectures may be needed.

SAMMANFATTNING (ABSTRACT IN SWEDISH)

Bakgrund Laparoskopisk kolecystektomi är en av de vanligaste bukoperationerna – ca 9000 kolecystektomier utförs årligen i Finland. Konversion till öppen operation, gallgångsskador samt postoperativa komplikationer försämrar dock alla patientens livskvalité. Vetskap om riskfaktorer för komplikationer, tillräckliga årliga operationsmängder och säkra metoder för gallgångsidentifikation (som t.ex. "Critical View of Safety" (CVS)) bidrar till högre vårdstandard.

Målsättning Avhandlingen strävade till att kartlägga riskfaktorer för konversion och postoperativa komplikationer i laparoskopisk kolecystektomi utförd för akut kolecystit. Därutöver strävade den till att undersöka hur kirurgernas erfarenhet samt årliga operationsmängd associerades med konversion, postoperativa komplikationer och operationstid. Slutligen strävade avhandlingen till att utreda associationen mellan CVS och gallgångsskador samt att utreda användningen av CVS bland enskilda kirurger.

Metoder Alla studier utfördes på Helsingfors Centralsjukhus. I Studie I ingick 373 patienter behandlade för akut kolecystit under 2013–2014. Multivariabel logistisk regression användes för att identifiera riskfaktorer för konversion och postoperativa komplikationer. Studie II analyserade retrospektivt 892 patienter behandlade för akut kolecystit under 2013–2016. Kirurger jämfördes gällande årlig operationsvolym (> 5 laparoskopiska kolecystektomier årligen *vs.* ≤ 5 laparoskopiska kolecystektomier årligen) samt gällande erfarenhet (specialiserande *vs.* specialist). I Studie III & IV tog kirurgerna stillbilder innan de klippte *ductus cysticus* och *arteria cystica*. Halvvägs genom studierna gavs en föreläsning om säker kolecystektomi. 4 kirurger poängsatte fotografierna enligt hur bra CVS uppnåddes. I Studie III utvärderades associationen mellan godkänd CVS och gallgångsskador samt postoperativa komplikationer. I Studie IV jämfördes mängden godkända CVS, gallgångsskador och postoperativa komplikationer bland specialiserande läkare och specialistläkare. Effekten av föreläsningen på godkänt CVS och andelen fotograferade kolecystektomier utvärderades också i Studie IV.

Resultat I Studie I konverterades 84 (22.5%) av 373 patienters kolecystektomi från laparoskopisk till öppen. Multivariabel logistisk regression identifierade C-reaktivt protein over 150mg/l, ålder över 65 år, diabetes, gangren av gallblåsan och abscessbildning som riskfaktorer för konversion. 67 (18.0%) patienter fick postoperativa komplikationer. Ålder över 65, manligt kön, njursvikt och konversion identifierades som riskfaktorer för postoperative komplikationer. I Studie II opererade kirurger med hög årlig operationsmängd snabbare än dem med låg årlig mängd (91 min *vs.* 108 min, p<0.001). Specialister med hög årlig operationsmängd konverterade mer sällan (14.9% *vs.* 32.0%, p<0.001) och opererade snabbare (95 min *vs.* 108 min, p<0.001) jämfört med specialister med låg operationsmängd. I Studie III

ingick 1532 patienter, varav 254 (23.1%) hade godkänt CVS, 823 (53.7%) hade icke-godkänt och 355 (23.2%) saknade fotografier. Patienter med godkänt CVS hade lägst andel gallgångsskador jämfört med patienter med icke-godkänt CVS eller saknande fotografier (0.3% *vs.* 1.0% *vs.* 2.3%, p=0.012). Patienter med godkänt CVS hade även lägst andel postoperativa komplikationer jämfört med patienter med icke-godkänt CVS eller avsaknad av fotografier (4.8% *vs.* 7.9% *vs.* 9.9%, p=0.011). I Studie IV hade specialiserande läkare högre andel av godkänt CVS i elektiva kolekystectomier (34.9% *vs.* 23.0%, p<0.001), men inte i akuta kolecystektomier (18.4% *vs.* 15.0%, p=0.252). Inga märkbara skillnader i gallgångsskador eller postoperativa komplikationer noterades mellan specialiserande läkare och specialister. Efter föreläsningen steg andelen fotograferade operationer från 74.0% till 80.3%, p=0.032 bland elektiva kolecystektomier, men akuta kolecystektomier påverkades inte märkbart. Ingen skillnad i andelen godkänd CVS, gallgångsskador eller postoperative komplikationer noterades före och efter föreläsningen.

S*lutsatser* Komplicerad kolecystit med högt CRP, gangren eller abscess höjer risken för konversion. Konversion höjer risken för postoperative komplikationer. Specialister som utför > 5 kolecystektomier för akut kolecystit årligen hade kortare operationstider och lägre konversionsrisk. Centralisering av operativ vård av akut kolecystit till färre specialister kan leda till bättre resultat. Intraoperativ fotografering av godkänt CVS är associerat med lägre andel av gallgångsskador och postoperativa komplikationer. För att öka andelen godkänd CVS krävs starkare åtgärder än enstaka föreläsningar.

TIIVISTELMÄ (ABSTRACT IN FINNISH)

Tausta Laparoskooppinen kolekystektomia on yksi tavallisimmista vatsanalueen leikkauksista – Suomessa tehdään vuosittain n. 9000 kolekystektomiaa. Kolekystektomiapotilaan elämänlaatu huononee konversioista avoimeen leikkaukseen, sappitievaurioista sekä postoperatiivisista komplikaatioista. Riittävä tietämys komplikaatioiden riskitekijöistä, turvallisten sappiteiden tunnistamismenetelmien (kuten Turvallisen näkymän) käyttö sekä riittävä kirurgin leikkauskokemus parantavat hoidon laatua.

Tavoitteet Väitöskirjan tavoitteena oli selvittää riskitekijöitä konversiolle ja postoperatiivisille komplikaatioille akuutin kolekystiitin vuoksi tehdyssä laparoskooppisessa kolekystektomiassa. Lisäksi tavoitteena oli tutkia kirurgien kokemuksen sekä vuosittaisten leikkausmäärien yhteyttä konversioon, postoperatiivisiin komplikaatiohiin ja leikkausaikaan. Lopuksi väitöskirja tutki Turvallisen näkymän yhteyttä sappitievaurioihin sekä kartoitti Turvallisen näkymän käyttöä kirurgien keskuudessa.

Menetelmät Tutkimukset tehtiin Helsingin yliopistollisessa keskussairaalassa. Osatyö I koostui vuonna 2013–2014 373 akuutin kolekystiitin vuoksi hoidetusta potilaasta. Riskitekijöitä konversiolle ja postoperatiivisille komplikaatioille kartoitettiin logistisen regression monimuuttujamallilla. Osatyö II:ssa analysoitiin retrospektiivisesti 892 vuosina 2013–2016 akuutin kolekystiitin vuoksi hoidettua potilasta. Kirurgeja vertailtiin vuosittaisen leikkausmäärän (>5 laparoskooppista kolekystektomiaa akuutin kolekystiitin vuoksi/vuosi *vs.* ≤ 5 kolekystektomiaa/vuosi) sekä erikoistumisen (erikoistuva *vs.* erikoislääkäri) suhteen. Osatyö III:ssa & IV:ssä kirurgit kuvasivat näkymää ennen sappirakkojohtimen ja -valtimon katkaisemista kolekystektomioissa vuosina 2018–2019. Maaliskuussa 2019 pidettiin luento turvallisesta kolekystektomiasta. Osatyö III:ssa arvioitiin Turvallisen näkymän yhteyttä sappitievaurioihin ja postoperatiivisiin komplikaatioihin. Osatyö IV:ssä vertailtiin erikoistuvien ja erikoislääkäreiden välillä Turvallisen näkymän käyttöä, sappitievaurioita ja postoperativiisia komplikaatioita. Lisäksi arvioitiin interventioluennon vaikutusta kuvattujen toimenpiteiden määrään ja Turvallisen näkymän oikeaoppiseen käyttöön.

Tulokset Osatyö I:ssä, 373 potilaasta 84 (22.5%) potilaan leikkaus konvertoitiin avoleikkaukseksi. Monimuuttujamallissa C-reaktiivinen proteiini yli 150 mg/l, ikä yli 65, diabetes, sappirakon gangreena ja absessi muodostuivat riskitekijöiksi konversiolle. 67 potilasta (18.0%) sai postoperatiivisia komplikaatioita. Ikä yli 65, miessukupuoli, munuaisten vajaatoiminta ja konversio muodostuivat riskitekijöiksi postoperatiivisille komplikaatioille. Osatyö II:ssa, korkean vuosittaisen leikkausvolyymin kirurgit leikkasivat nopeammin verrattuna matalan leikkausvolyymin kirurgeihin (91min *vs.* 108 min, p <0.001). Verratessa vain erikoislääkäreitä, todettiin, että korkean volyymin erikoislääkärit konvertoivat vähemmän

(14.9% *vs.* 32.0%, p<0.001) ja leikkasivat nopeammin (91 min *vs.* 108 min, p<0.001) kuin matalan volyymin erikoislääkärit. Osatyö III koostui 1532 potilaasta, joilla 354:llä (23.1%) oli hyväksyttävä Turvallinen näkymä, 823:lla (53.7%) oli ei-hyväksyttävä Turvallinen näkymä, ja 355 potilaalta (23.2%) puuttui valokuvat. Potilailla, joilla oli hyväksyttävä Turvallinen näkymä oli matalin sappitievaurio-osuus verrattuna ei-hyväksyttävän Turvallisen näkymän ja puuttuvien valokuvien potilaisiin (0.3% *vs.* 1.0% *vs.* 2.3%, p=0.012). Potilailla, joilla oli hyväksyttävä Turvallinen näkymä oli myös matalin postoperatiivisen komplikaatioiden osuus ei-hyväksyttävän Turvallisen näkymän ja puuttuvien valokuvien potilaisiin (4.8% *vs.* 7.9% *vs.* 9.9%, p=0.011). Osatyö IV:ssä erikoistuvilla oli suurempi osuus hyväksyttävää Turvallista näkymää elektiivisissä kolekystektomioissa verrattuna erikoislääkäreihin (34.9% *vs.* 23.0%, p<0.001), mutta ei päivystyskolekystektomioissa (18.4% *vs.* 15.0%, p=0.252). Merkitseviä eroja sappitievaurioissa tai postoperatiivisissa komplikaatioissa ei ilmennyt erikoistuvien ja erikoislääkäreiden välillä. Luennon jälkeen elektiivisiä kolekystektomioita valokuvattiin enemmän (80.3% *vs.* 74.0%, p=0.032). Luennolla ei ollut vaikutusta Turvallisen näkymän käyttöön, sappitievaurioihin tai postoperatiiviisin komplikaatioihin.

Päätelmät Vaikea kolekystiitti korkeine CRP-arvoineen, gangrenoineen ja absesseineen nostaa konversioriskiä. Konversio lisää postoperatiivisten komplikaatioiden todennäköisyyttä. Erikoislääkäreillä, jotka leikkaavat yli 5 kolekystiittiä vuodessa, on lyhyemmät leikkausajat ja konversio-osuudet. Akuutin kolekystiitin leikkaushoidon keskittäminen pienemmälle määrälle erikoislääkäreitä voisi parantaa tuloksia. Leikkauksenaikaisen turvallisen näkymän valokuvadokumentaatio on yhteydessä matalampaan sappitievaurioiden ja postoperatiivisia komplikaatioiden määrään. Turvallisen näkymän käytön lisäämiseksi tarvitaan vahvempia keinoja kuin yksittäisiä luentoja.

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications, referred to in the text by Roman numerals, and reproduced with the permission of their copyright holders.

I. **Terho P, Leppäniemi A, Mentula P**. Laparoscopic Cholecystectomy for Acute Calculous Cholecystitis: A Retrospective Study Assessing Risk Factors for Conversion and Complications. *World J Emerg Surg*. 2016 16;11:54.

II. **Terho P, Sallinen V, Leppäniemi A, Mentula P**. Does the Surgeon's Caseload Affect the Outcome in Laparoscopic Cholecystectomy for Acute Cholecystitis? *Surg Laparosc Endosc Percutan Tech*. 2020 30:522-528.

III. **Terho P, Sallinen V, Lampela H, Harju J, Koskenvuo L, Mentula P**. The Critical View of Safety and Bile Duct Injuries in Laparoscopic Cholecystectomy: A Photo Evaluation Study on 1532 Patients. *HPB (Oxford)*. 2021 23:1824-1829.

IV. **Terho P, Sallinen V, Lampela H, Harju J, Koskenvuo L, Mentula P**. The Critical View of Safety in Laparoscopic Cholecystectomy: User Trends among Residents and Consultants. *Surg Laparosc Endosc Percutan Tech*. 2022 32:453-461

ABBREVIATIONS

APACHE	Acute Physiology and Chronic Health Evaluation
ASA	American Society of Anesthesiologists
BDI	Bile Duct Injury
CBD	Common Bile Duct
CCI	Comprehensive Complication Index
CHD	Common Hepatic duct
CI	Confidence Interval
CRP	C-Reactive Protein
CT	Computed Tomography
CVS	Critical View of Safety
ERC	Endoscopic Retrograde Cholangiography
ESWL	Extracorporeal Shock Wave Lithotripsy
ICD	International Classification of Diseases
ICG	Indocyanine Green
INR	International Normalized Ratio
IOC	Intraoperative Cholangiography
IQR	Interquartile range
GI	Gastrointestinal
LCC	Laparoscopic Cholecystectomy
MRI	Magnetic Resonance Imaging
MRCP	Magnetic Resonance Cholangiography
OC	Open Cholecystectomy
OR	Odds Ratio
PT	Prothrombin Time
QoL	Quality of Life
RCT	Randomised Controlled Trial
RHA	Right Hepatic Artery
RUQ	Right Upper Quadrant
SSI	Surgical Site infection
US	Ultrasound
WBCC	White blood cell count

1 INTRODUCTION

Laparoscopic cholecystectomy (LCC) performed for biliary colic, acute cholecystitis, and biliary pancreatitis, among other indications, is one of the most common abdominal operations. Approximately 9000 and 66 000s LCCs are annually performed in Finland and the UK, respectively (1,2). Thus, the quality of LCC annually affects the quality of life (QoL) of hundreds of thousands of patients worldwide. The following sections will evaluate factors that influence the quality of LCC.

Ideally, cholecystectomy should be performed laparoscopically, since open cholecystectomy is associated with more postoperative pain, more wound complications and longer hospital-stay (3-5). Furthermore, open cholecystectomy predisposes to long-term adhesion related morbidity (6). However, if LCC proves too difficult, the surgeon might convert to an open procedure. The risk of conversion is significantly higher in emergency LCC for acute cholecystitis than in elective LCC (7). Despite widespread use of LCC for over 30 years, conversion rates vary from 5-30% for acute cholecystitis, depending on patient risk factors and differences in surgical management (7-12). In this thesis, Study I aimed at identifying risk factors for conversion and postoperative complications in LCC for acute calculous cholecystitis.

Bile duct injuries (BDIs) in LCC are rare with an overall incidence of 0.3-1.8% (12-17), but with LCCs performed in such high numbers, BDIs substantially contribute to lowered QoL and excess health-care expenses. Severe BDI can at its worst require future liver transplantation or lead to death of the patient. Some BDIs will inevitably occur under difficult conditions, yet other injuries arising from insufficient dissection and identification, might be prevented. To prevent misidentification of anatomy and major BDIs, hepatopancreaticobiliary surgeons Strasberg *et al.* proposed an identification method called the Critical View of Safety (CVS) in 1995 (18). Guidelines recommend CVS, as no major BDIs have been associated with its correct use (15,19-23). However, according to surveys, surgeons still frequently use other identification techniques (24,25). Furthermore, assessing CVS based on operative notes alone is unreliable, and intraoperative photos or videos might be preferable. Study III aimed at investigating if intraoperative photos of CVS were associated with the incidence of BDIs and postoperative complications. Study IV aimed at investigating correct use of CVS among individual surgeons.

The skills of surgeons performing LCC naturally influence the outcome. Residents should have sufficient experience before performing LCC for acute cholecystitis alone and need continuous repetition to maintain acquired skills. Due to more challenging circumstances in acute cholecystitis, some studies recommend that only consultants should perform LCC for acute cholecystitis, or supervise residents performing LCC (26,27). Study II aimed to assess the association of surgeons' experience and annual caseloads with conversion, operating time, and postoperative complications in LCC for acute cholecystitis.

2 REVIEW OF THE LITERATURE

2.1 GROSS ANATOMY AND PHYSIOLOGY OF THE BILIARY TRACT

The gallbladder is a hollow, pear-shaped organ located inferiorly of the right lobe of the liver. It measures around 7 to 10 cm in length and 2.5 to 3.5 cm in width, and is divided into three sections: the fundus, the body, and the neck. The body lies in the gallbladder fossa (aka the cystic plate) of the liver, at the junction of segments IVB and V. The gallbladder acts as a reservoir for bile and normally holds a volume of 30 to 50 ml but may become remarkably distended under pathological conditions. Bile mainly contains bile acids, phospholipids, cholesterol, and bilirubin - an excess product following the breakdown of hemoglobin (28). Following food intake, the gallbladder contracts, releasing the bile into the intestine, where it emulsifies lipids in food and aids in their enzymatic digestion (29). The hepatocytes of the liver produce around 400 to 800 ml of bile daily.

Bile flows from the liver to the gallbladder via the extrahepatic bile ducts. The right and left hepatic ducts join inferiorly of the liver, creating the common hepatic duct (CHD). The gallbladder is connected to the CHD via the cystic duct (*ductus cysticus*) at the neck of the gallbladder. At the junction of the neck of the gallbladder and the cystic duct, is an outpouching of the gallbladder wall called Hartmann's pouch as described by French surgeon Henri Hartmann in his anatomical descriptions in 1891 (30). The cystic duct usually joins the common hepatic duct at around 3 cm from the liver confluence to form the ~8 cm long common bile duct (CBD, *ductus choledochus*), which runs anteriorly to the portal vein and ends in the duodenum at the ampulla Vater (31). The muscular sphincter of Oddi controls bile flow into the duodenum.

The cystic artery (aka the bachelor artery, *arteria cystica*) supplies the gallbladder. In around 70% of individuals, it arises from the right hepatic artery and runs superiorly to the cystic duct. (32,33). At the neck of the gallbladder, the cystic artery divides into the superficial branch, which runs over the left-hand side of the gallbladder, and the deep branch, which runs between the gallbladder and the gallbladder fossa

Lymph drains from the gallbladder via the cystic node (aka Calot's node), situated between the cystic duct and the common hepatic duct. From there, the lymph drains into lower hepatic lymph nodes that drain into celiac lymph nodes (34).

The hepatocystic triangle is an important surgical landmark for it contains the cystic artery and duct. It is comprised of the inferior margin of the liver superiorly, the CHD medially, and the cystic duct and the neck of the gallbladder laterally. The hepatocystic triangle is commonly referred to as Calot's triangle, which, however, in its original description by the French

surgeon Calot in 1891 (35,36), similarly had borders made up of the cystic duct and the CHD, but the superior border was made up of the cystic artery. This thesis will refer to Calot's triangle in its original meaning.

Among other important surgical landmarks, is Rouviere's sulcus, first described by the French anatomy professor Henri Rouviere in 1924 (37). The sulcus is 2 to 5 cm long and runs anterior to the caudate process, laterally to the liver hilum. Rouviere's sulcus indicates the plane of the CBD. Calot's triangle, along with the cystic duct and artery, is found anterosuperiorly to the sulcus, where dissection is safe (38).

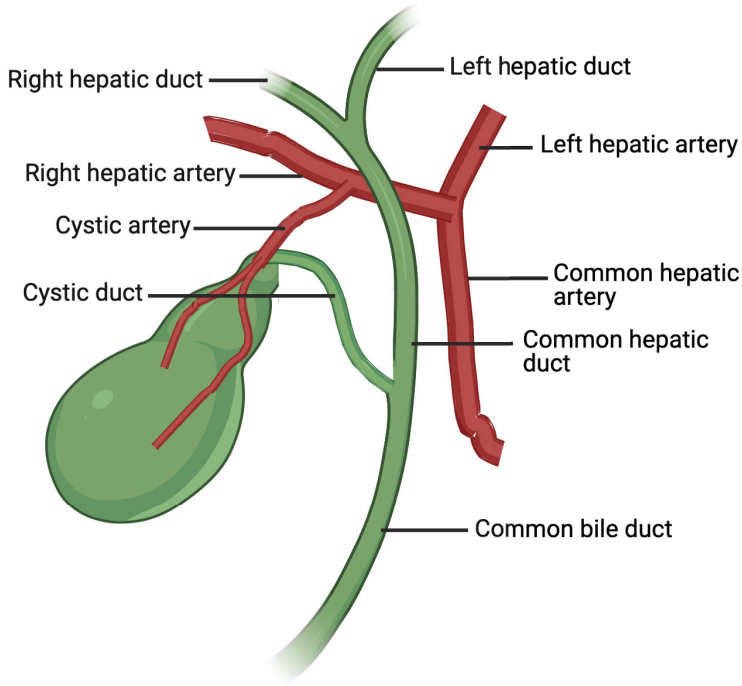

Fig 1. The typical anatomy of the biliary system.

2.1.1 VARIATIONS IN BILIARY TRACT ANATOMY

Variations in biliary anatomy are common, and failure to recognize them is a common source of BDI in cholecystectomy. Less than 50% of individuals present with the "typical" anatomy; a single gallbladder, a single 2 to 3 cm long cystic duct joining the CHD at around 3 cm from the liver confluence, and a single cystic artery originating from the right hepatic artery running superiorly to the cystic duct (31,39). Therefore, knowledge of variations is important for

gastrointestinal (GI) surgeons, who are bound to encounter them throughout their career.

BILE DUCT VARIATIONS

The section below will present some of the most common clinically relevant variations in cystic duct anatomy (31,40,41).

a) In 10-20% of individuals, the cystic duct is abnormally long and fuses with the CHD at a low site. The cystic duct is then frequently closely adhered to the CHD, raising the risk of injury to the CHD.

b) The cystic duct may be abnormally short, or the neck of the gallbladder may be directly connected to the CHD, making clipping the cystic duct or neck of the gallbladder without injury to the CHD or CBD hard.

c) In around 2% the cystic duct joins the CHD unusually high.

d) In 1% of individuals, the cystic duct connects directly to the right hepatic duct. In this and the previous scenario, the left and especially the right hepatic ducts run a raised risk of injury.

e) An accessory cholecystohepatic duct is present in around 1% of individuals, connecting to the body of the gallbladder and draining parts of the right lobe of the liver. Failure to ligate this duct in cholecystectomy might result in bile leak.

Moreover, the cystic duct mostly connects to the CBD laterally, but it may also insert anteriorly, posteriorly, or medially.

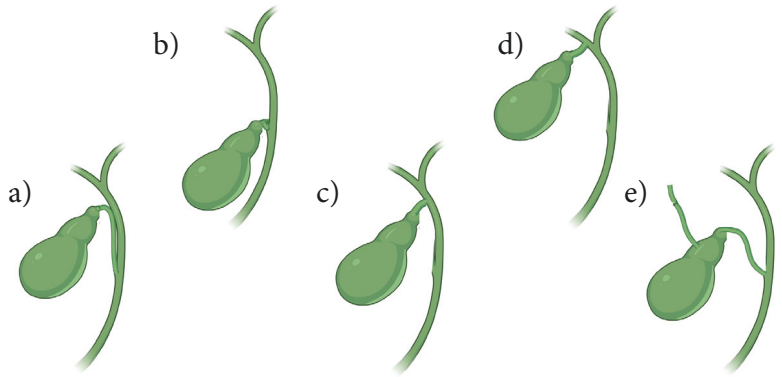

Figure 2. Cystic duct variations

In the literature, the terms subvesical duct, aberrant duct, accessory duct and duct of Luschka are often used synonymously (42,43). Subvesical ducts comprise both aberrant and accessory ducts, and they are encountered in around 4% of individuals (42,44). In this thesis, accessory ducts refer to ducts that drain part of the liver (usually segments of the right lobe) and may insert into the gallbladder (cholecystohepatic duct), cystic duct, the right hepatic duct or the CHD. Failure to identify these ducts may cause

bile leak and ligation may cause bile obstruction. Aberrant ducts refer to small bile ducts encountered in the connective tissue of the gallbladder fossa attaching to the gallbladder. Damage to these ducts may result in postoperative bile leak. The term 'duct of Luschka' should be avoided, as it in its original meaning (as described by German anatomist Herbert Luschka in 1863) described microscopic bile ducts in the liver parenchyma, which in light of today, may have been lymphatic vessels (42).

Furthermore, some bile duct variations requiring extreme measures during cholecystectomy may be encountered. For example, very rarely (<0.1%), the left and right hepatic ducts drain directly into the gallbladder, with the common bile duct continuing straight from the gallbladder, making cholecystectomy without bile duct anastomosis impossible (44).

VASCULAR VARIATIONS

Vascular variations are more common that ductal variations. Approximately 50% of patients present with variations in the anatomy of the cystic artery or the hepatic arteries. The following clinically relevant vascular variations of the cystic artery have been recognized (31,39,45).

a) An accessory or double cystic artery arising from the right hepatic artery is present in 15-20% of individuals. Triple arteries are found in around 1% of individuals.

b) In 5-15% of individuals, the right hepatic artery runs through Calot's triangle, giving off the cystic artery superiorly, making the right hepatic artery a target for accidental ligation, if confused with the cystic artery. Damage to the artery during surgery might cause profuse bleeding while its ligation might lead to liver ischemia.

c) Rarely, the cystic artery runs anteriorly to the CBD and hence it usually needs to be divided first when encountered to obtain adequate exposure of the hepatocystic triangle**.**

d) In 5% of individuals, the cystic artery runs inferiorly to the cystic duct.

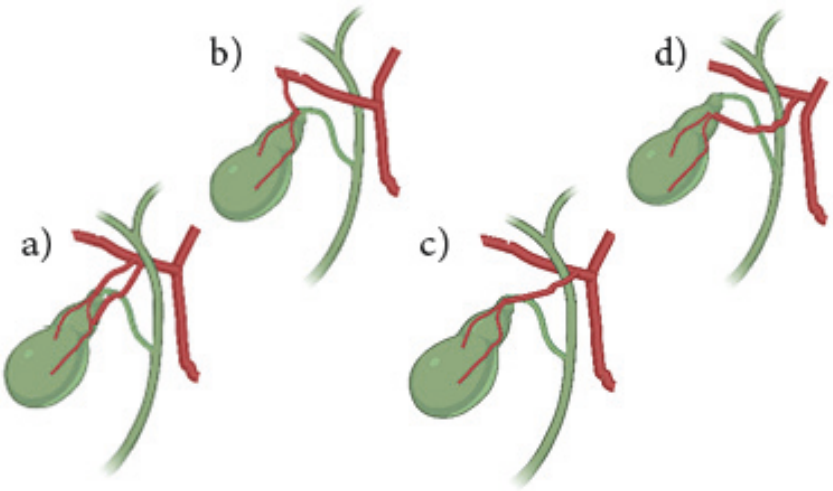

Figure 3. Cystic artery variations

GALLBLADDER VARIATIONS

Gallbladder anomalies may be congenital or arise due to pathological processes. Some of them might in themselves cause symptoms or severely complicate the removal of the gallbladder. The following gallbladder anomalies relevant to cholecystectomy are listed.

Gallbladder duplication is extremely rare, occurring in approximately 1 of 4000 persons (46). Two gallbladders with their own cystic ducts fusing with the CHD exist. As asymptomatic, the condition requires no treatment, but should one of the gallbladders become diseased, it is advised to remove both during the same operation.

A floating gallbladder is usually encountered in women over 60 years, and occurs in approximately 5% of patients (47). The gallbladder is surrounded by peritoneum and is hanging from the liver fossa instead adhering to it. This predisposes the gallbladder to torsion around itself, resulting in ischemia and necrosis, requiring cholecystectomy.

An intrahepatic gallbladder is usually partially (and rarely completely) embedded within the liver parenchyma (48).

A retrodisplaced gallbladder is not situated in the gallbladder fossa of the liver but is suspended from another part of the liver with the fundus situated posteriorly. The gallbladder might then be located retroperitoneally, complicating its removal (49).

2.2 BENIGN GALLBLADDER DISEASE

2.2.1 GALLSTONE DISEASE AND BILIARY COLIC

Around 5-30% of the adult population has gallstones (50-52). Gallstones are more common in developed countries, and studies on Nordic countries report a prevalence of 15% in the population (50,52,53). Age is a strong risk factor for gallstones, and approximately over 40% of over 70-year-olds in developed countries have gallstones (54). Other risk factors include female sex, ethnicity, diabetes, rapid weight loss, pregnancy and metabolic syndrome (50,51,54,55). Gallstones are asymptomatic in most patients, but in prospective follow-up studies, around 20% of individuals with initially asymptomatic gallstones developed symptoms or complications within 10 years from diagnosis (56,57).

2.2.1.1 PATHOPHYSIOLOGY OF GALLSTONE DISEASE

Cholesterol and pigment stones are the two main types of gallstones. Around 80% of all gallstones are cholesterol stones (58). They are formed from supersaturation of bile with cholesterol, which then crystallizes into stones (59). The stone formation is further affected by decreased motility in the biliary tract precipitated by age. Pigment stones account for around 20% of gallstones. They usually form in individuals with chronic liver disease or hemolytic conditions, and consist of calcium salt and bilirubin (58). Pigment stones seem to originate within the intrahepatic and extrahepatic bile ducts, from where they become dislodged into the gallbladder.

2.2.1.2 DIAGNOSIS OF GALLSTONE DISEASE

Gallstones may remain asymptomatic for a long time. According to studies, biliary colic caused by gallstones is located in the epigastrium, or the right upper quadrant (RUQ), builds up to a steady level, lasts more than 30 minutes, is severe enough to interrupt daily activities, and is not significantly related to bowel movements or relieved by postural change or acid suppression (60,61). The pain may be associated with nausea and radiation to the back and might interrupt sleep. Clinical status and laboratory parameters are normal in uncomplicated gallstone disease. Biliary colic presenting without gallstones is considered functional and called biliary dyskinesia. It presents with an incidence of around 1.7/10 000 persons (62).

Typical symptoms listed above usually raise suspicion of gallstones, but they may also be found by chance in imaging performed for other reasons. Of imaging modalities, ultrasound (US), computed tomography (CT) and magnetic resonance imaging (MRI) are applicable.

US is the gold standard of imaging recommended for the diagnosis of biliary pathology and gallstones, with a sensitivity around 0.85-0.98 and 0.97-0.99 specificity for suspected gallstones (63-65). It is noninvasive, inexpensive, and available at most medical centers. US is also superior to computed tomography (CT) at detecting stones in the gallbladder, but its disadvantages lie in the limited visibility of the CBD. Dilation of the

intrahepatic ducts is, however, readily visible on US and is indicative of CBD stones in combination with acute RUQ pain and jaundice.

For detecting gallstones, CT sensitivity has been reported at 0.5-0.6 and specificity at around 0.9 (66,67). Furthermore, CT is associated with significant levels of radiation. The advantages of CT lie in its broad and fast availability. Moreover, in diagnosing complications of gallstone disease such as biliary pancreatitis or complications of acute cholecystitis, CT has higher diagnostic accuracy.

MRI in the form of magnetic resonance cholangiography (MRCP) is used especially for detecting stones in the bile ducts with a sensitivity of 0.9 and specificity of 1.0 (68). Its disadvantages lie in high-cost and limited availability.

2.2.1.3 TREATMENT OF GALLBLADDER STONES

The recommended treatment for symptomatic gallbladder stones is laparoscopic cholecystectomy (LCC) (69). Early LCC performed within days from diagnosis of biliary colic results in decreased morbidity compared with LCC months later (70), but in practice, most LCCs in Finland are performed as ambulatory surgery within six-months of diagnosis. Certain dietary restriction like avoiding fatty foods might ease the symptoms of gallstone disease (71).

Alternative approaches from surgery includes dissolving of gallstones using chenodiol or ursodeoxicol (72,73). This treatment is rarely used nowadays due to limited effect but may be an alternative in symptomatic patients with contraindications for surgery. Furthermore, extracorporeal shockwave lithiotropsy (ESWL) has been effective in breaking down gallbladder stones, but due to high recurrence of stones following initial ESWL, many patients require LCC in the end, an thus, ESWL might be recommended only for patients unfit for surgery (74).

Around 20% of patients undergoing LCC for gallstones do not experience relief from the treatment and are considered to suffer from "postcholecystectomy syndrome" (75). No obvious cause has been found in 20% of patients with postcholecystectomy syndromes, whilst others' symptoms have later been attributable to and resolvable with treatment of peptic ulcer disease, pancreatitis, *H. pylori* infection or retained bile duct stones (75). Nevertheless, biliary dyskinesia without gallstones might be treated with LCC as according to a meta-analysis on randomized trials, patients suffering from biliary dyskinesia experienced symptoms relief following LCC as well (76).

No randomized controlled trials on how to treat asymptomatic aka "silent" gallstones have been conducted (77). In a longitudinal study on over 10 years, 25.8% of patients with initially asymptomatic gallstones developed biliary colic, and 3.0% developed a gallstone-related complication (56). Nevertheless, LCC for silent gallstones might be favorable in patients of certain ethnicities (such as Native Americans) or with stones over 3cm in

diameter due to raised risk of developing gallbladder carcinoma (78). In the recent decade, LCCs performed for acute cholecystitis have decreased by 20% due to LCCs being performed with a lower threshold for biliary colic (79).

2.2.2 ACUTE CHOLECYSTITIS

Acute cholecystitis is a somewhat rare complication of gallstones, as less than 5% of patients develop cholecystitis within 15 years of detection of gallstones (80,81).

Acute cholecystitis usually presents with prolonged RUQ pain and fever. Risk factors for acute cholecystitis are age, diabetes, obesity and male sex (82,83). Acute cholecystitis still carries an overall 3-4% risk of mortality even with today's treatment (84,85)

Two international guidelines – The Tokyo Guidelines and The World Society of Emergency Surgery Guidelines – give recommendations on the diagnosis and treatment of acute cholecystitis (86-88).

2.2.2.1 PATHOPHYSIOLOGY OF ACUTE CHOLECYSTITIS

In acute cholecystitis, the cystic duct is obstructed by gallstones, leading to build up of bile and bacteria in the gallbladder. The most commonly found pathogens in biliary infections are *Eschericia coli*, *Klebisella pneumonia* and *Bacteroides fragilis* (89). When the inflammation progresses, the gallbladder wall might become necrotic, leading to perforation and generalized peritonitis. Rarely, gallbladders may become inflamed without the presence of gallstones. This "acalculous cholecystitis" occurs with an incidence of less than 5% and is common in critical care patients (90).

2.2.2.2 DIAGNOSIS OF ACUTE CHOLECYSTITIS

Clear diagnostic criteria are needed to distinguish patients with acute cholecystitis from those with benign RUQ pain, who may be discharged from the emergency room. Diagnosis of acute cholecystitis should be based on patient history, clinical status, and laboratory and imaging findings. In a systematic review and meta-analysis by Trowbridge *et al.*, no specific clinical sign or laboratory test was sufficient enough to validate or rule out a diagnosis of acute cholecystitis (91).

According to the 2018 Tokyo guidelines (87), diagnosis of acute cholecystitis is based on

A Clinical findings such as
    1. Murphy's sign,
    2. RUQ mass/pain/tenderness
B Systemic signs of inflammation such as
    1. Fever
    2. elevated C reactive protein (CRP)
    3. elevated WBCC (white blood cell count)
C Imaging findings characteristic of acute cholecystitis.

One item in A and one item in B validate a suspected diagnosis of acute cholecystitis, and imaging is recommended.

The 2020 World Society of Emergency Surgery Guidelines recognize the Tokyo Guideline criteria as useful, yet question their diagnostic capacity, as validation studies have demonstrated limited accuracy (86). In a retrospective analysis, Naidu *et al.* found that the Tokyo Guidelines criteria with US as imaging correctly identified 83.1% of patients with histopathologically confirmed acute cholecystitis, but gave false positives to 62.5% without cholecystitis (92) whilst, Joseph *et al.* found that the Tokyo Guidelines had a 53% sensitivity for patients with later histopathologically confirmed acute cholecystitis (93).

For confirming a clinical diagnosis of acute cholecystitis, US is recommended as the first line of imaging. US is not the most sensitive imaging modality as according to a meta-analysis on imaging modalities, the summary sensitivity of US for acute cholecystitis was 81% and specificity 83% (94). However, its lack of ionizing radiation and general availability still makes US the preferred first imaging for suspected acute cholecystitis (94,95). US is diagnostic for acute cholecystitis. if gallstones and inflammatory changes on the gallbladder are visible. However, if the patient is septic, or there is a strong suspicion of gangrenous or emphysematous cholecystitis, contrast-enhanced CT is recommended, since US might be inconclusive, and the delay to surgery caused by imaging is usually shorter with the use of CT (96). Furthermore, CT would be recommended in scenarios, where cholecystitis is not the primarily suspected diagnosis. A negative US should also be followed up by CT in patients with suspicion of acute cholecystitis. In a prospective study, Fagenholtz *et al.* reported a sensitivity of 92% for CT compared with 79% for US ($p=0.015$) for diagnosing acute cholecystitis (97). Likewise in patients with strong suspicion of bile duct stones due to elevated transaminases or jaundice, MRCP should be performed in combination with or without US (98).

Based on clinical, laboratory and imaging findings, the Tokyo Guidelines grade acute cholecystitis as grade I-III (mild, moderate, severe), and treatment recommendations are based on the severity of the inflammation as described in Table 1.

TABLE 1. Severity of acute cholecystitis according to the Tokyo Guidelines.

GRADE I – MILD ACUTE CHOLECYSTITIS

Acute cholecystitis in a healthy patient with mild inflammatory changes on the gallbladder and without organ dysfunction

GRADE – MODERATE ACUTE CHOLECYSITITS

Associated with any of the following findings:

1. Elevated WBCC >18,000/mm^3
2. Palpable tender mass in RUQ
3. Symptoms duration >72h
4. Notable local inflammation (gangrenous or emphysematous inflammation, pericholecystic or hepatic abscess, biliary peritonitis)

GRADE III – SEVERE ACUTE CHOLECYSTITIS

Associated with any of the following findings:

1. Cardiovascular dysfunction: hypotension requiring dopamine > 5ug(kg/min or any dose of noradrenaline
2. Neurological dysfunction: decreased level of consciousness
3. Respiratory dysfunction PaO2/FiO2 ratio < 300
4. Renal dysfunction: oliguria, creatinine > 2.0mg/dl
5. Hepatic dysfunction: PT-INR >1.5
6. Hematological dysfunction: platelet count < 100,000/mm^3

INR International normalized ratio PT Prothrombine time

2.2.2.3 SURGICAL TREATMENT OF ACUTE CHOLECYSTITIS

Patients eligible for surgery and presenting with acute cholecystitis should undergo LCC during the index admission, since the risk of other biliary complications has been reported at 19% in the following 12 weeks in patients treated conservatively (99). The Tokyo Guidelines base their treatment recommendations of acute cholecystitis on the severity grading (100).

All patients should receive initial general supportive care (88) with analgesics, fluid administration and antimicrobial therapy (101). Treatment should be initiated without specific diagnosis if the patient is critically ill. Blood pressure, urine output, respiratory rate and heart rate should be monitored. If the initial therapy fails and the patient deteriorates, ICU admission and organ support should be considered. If possible, blood and bile cultures should be obtained; blood cultures before the initiation of antibiotics and bile cultures during surgery. Antimicrobial therapy should be initiated as soon as possible, especially in patients with septic shock, in whom antibiotics should be initiated within 1 h of examination (102).

In Grade I, early LCC is generally recommended. However, in case of severe comorbidity (Chalson Comorbidity Index (CCI) ≥ 6, American

Society of Anesthesiologists (ASA) > 3), antibiotics, general supportive care and observation are recommended initially, since CCI > 6 was significantly associated with increased 30-day mortality in patients who received emergent LCC in a cohort study on patients with acute cholecystitis (103).

In Grade II, antibiotics and general supportive care followed by early LCC are recommended. If the patient deteriorates despite antibiotics and supportive care, and has severe comorbidities, the Tokyo Guidelines recommend percutaneous gallbladder drainage followed by delayed LCC.

In Grade III, the patients already present with one or more organ dysfunctions due to systemic inflammation. Antibiotics and general organ support are the initial treatment. If the condition of the patients stabilizes enough for general anesthesia, early LCC can be considered. In case the patient deteriorates, percutaneous gallbladder drainage is recommended followed by delayed LCC. The guidelines stress that only laparoscopically advanced surgeons should perform LCC for patients with Grade III acute cholecystitis.

Initially, the Tokyo Guidelines from 2013 (104) were criticized for recommending a conservative approach in selected patients of Grade II and all Grade III patients, as studies demonstrated early surgical treatment to be feasible in Grade II-III patients (93,105). Therefore, the Tokyo Guidelines from 2018 expanded their recommendation to include surgery for selected patients of Grade III taken that a laparoscopically experienced surgeon was available (88). The World Society of Emergency Surgery 2020 guideline, recommends initial LCC for all patients fit for surgery regardless of the severity of cholecystitis (86).

Around 15% of patients with acute cholecystitis present with concomitant CBD stones (106). Stones may be diagnosed and treated pre-, intra- or postoperatively with endoscopic retrograde cholangiography (ERC) and sphincterotomy, or intraoperatively with cholangiography and CBD exploration. The 2020 World Society of Emergency Surgery Guidelines recommend treatment of CBD stone during the same admission, yet the optimal way of treatment remains unclear. In a meta-analysis, Vettoretto *et al.* found insufficient evidence to evaluate the effect of intraoperative ERC vs. preoperative ERC on morbidity or mortality, but intraoperative ERC lengthened operating time, whilst preoperative ERC seemed to lengthen hospital-stay (107). In their meta-analysis, Singh *et al.* found that laparoscopic CBD exploring was superior to preoperative ERC in terms of technical success and hospital stay (108). In a similar meta-analysis, however, Lyu *et al.* found that preoperative ERC resulted in better CBD clearance, decreased the risk of bile leak, but raised the risk for pancreatitis, whilst laparoscopic CBD exploring decreased the hospital stay (109).

Early LCC is recommended over delayed LCC for acute cholecystitis (110). Previously, acute cholecystitis was treated with antibiotics and delayed LCC was performed months later, as it was thought that the swollen, oedemic gallbladder would complicate the surgery. In a systematic review of discordant meta-analyses, early LCC reduced wound infections, hospitalization, operating time and raised QoL compared with delayed LCC

(111). This is probably attributable to the formation of adhesions and scarring following acute inflammation that do not resolve over time. However, many studies have defined early LCC as LCC within one week from admission, and it remains a question, whether how soon from admission patients with acute cholecystitis should be operated on, since the inflammation might progress remarkably in one week (112). According to a meta-analysis of randomized controlled trial (RCTs) on timing for LCC, surgery within the first 24 hours of admission did not lower the rate of postoperative complications. However, LCC within the first 72 hours from symptoms onset resulted in fewer conversions and postoperative complications (113). Symptoms duration might, however, not be a straightforward way of determining operating urgency, as especially in the elderly, cholecystitis may present without signs of peritoneal irritation leading to delayed diagnosis (114). Nevertheless, in an RCT on patients with symptoms duration >72 hours, early LCC was associated with less morbidity, shorter hospital stay, duration of antibiotic therapy, and reduced cost compared with delayed LCC (115). Therefore, early LCC may be recommended even with unknown symptoms duration.

2.2.2.4 NON-SURGICAL TREATMENT OF ACUTE CHOLECYSTITIS

Treatment options for patients unfit for or refusing surgery include antibiotics and general supportive care. In case of severe cholecystitis not resolving with antibiotics, percutaneous or endoscopic gallbladder drainage may be considered. Yet, defining which patients are unfit for surgery is not clear.

Several RCTs comparing early LCC with delayed LCC have been conducted in favor of early LCC (116), yet prospective studies on the long-term effects of conservative treatment over LCC are scarce. Conservative treatment may be an option in selected patients, yet it comes with a risk of recurring events. Schmidt *et al.* conducted a long-term follow-up RCT on patients with acute cholecystitis randomized to LCC (n=31) or best available therapy without surgery, (n=33) and found no differences in long-term mortality and complications over a median follow-up of 14 years (117). Of the conservatively treated patients, however, 33% experienced a new gallstone-related event and 33% required LCC, telling us early LCC would be favorable in terms of readmission. Furthermore, all patients presenting with peritonitis were excluded.

The Tokyo Guidelines recommend percutaneous transhepatic gallbladder drainage (PTGD) in some Grade II or III patients or patients too sick or elderly to undergo LCC (26). PTGD is contraindicated in patients with ascites or on anticoagulants, and significant complications related to it include bowel perforation, and biliary peritonitis following catheter dislodgement (118). Nevertheless, little high-quality evidence on treatment with PTGD over LCC in patients considered high risk due to underlying sickness or severe cholecystitis exists. In a systematic review on retrospective and observational studies Winbladh *et al.*, reported a 15.4% 30-day mortality for patients treated with drainage compared with 4.5% for those treated with LCC initially (119). Furthermore, 40% of patients treated with drainage had LCC later. The only

prospective randomized trial comparing LCC and percutaneous gallbladder drainage - the CHOCOLATE trial (120) - enrolled patients with acute physiological assessment and chronic health evaluation (APACHE) score II (121) of 7 or more, and found no significant difference in the groups in terms of mortality, but patients receiving LCC over PTGD had significantly fewer complications and reinterventions. Nevertheless, percutaneous gallbladder drainage is a viable option in septic patients with contraindications for surgery, as 93% of patients treated with PTGD in the CHOCOLATE trial showed clear clinical improvement in the following 48 hours (120). However, conservative treatment without PTGD might be underrated. In an RCT on high-risk patients (APACHE = or > 12), PTGD showed no advantage in terms of symptoms resolution or mortality compared with conservative treatment with antimicrobial and general supportive care (118). No other RCTs comparing PTGD and conservative treatment in high-risk patients exist.

Endoscopic gallbladder drainage (EGBD) has emerged as a treatment option in recent years. However, it requires high skill, which limits its availability. It may be performed as endoscopic transpapillary gallbladder drainage (ETGBD) or transmural ultrasonography-guided gallbladder drainage (EUS-GBD). In the transpapillary approach, either endoscopic nasogallbladder drainage (ENGBD) or endoscopic gallbladder stenting (EGBS) may be used. ENGBD and EGBS have proven effective in RCTs reporting pooled technical success rate of ENGBD of 80.9% and a pooled clinical response rate of 75.3%. For EGBS, the results were 96% and 88% respectively (122,123). In a meta-analysis comparing all EGBD techniques with PTGBD, no significant difference in technical success emerged, but likewise, EGBD was associated with fewer postoperative complications (124).

The 2020 World Society of Emergency Surgery Guidelines recommend delayed LCC for patients with initial conservative treatment after reduction in perioperative risk to decrease readmission for biliary events (86). Yet, no prospective trials comparing delayed LCC with observation in patients initially treated with PTGD exist. In a retrospective study by De Mestral *et al.,* 40% of PTGD patients received delayed LCC, and the readmission rate of PTGD patients treated without LCC was 49% at one year (99).

2.2.3 OTHER COMPLICATIONS OF GALLSTONE DISEASE

Among other complications of gallbladder stone disease, are biliary pancreatitis, bile duct stones and cholangitis as well as chronic cholecystitis (125).

In chronic cholecystitis, the gallbladder wall tends to be chronically inflamed. Chronic impaction of a stone in the gallbladder neck might result in Mirizzi's syndrome, as described by the Argentinian surgeon Pablo Mirizzi in 1948, where the continuous pressure on the common hepatic duct from the impacted stone or resulting fibrosis causes obstructive jaundice (126). Following stone impactation, a cholecystoduodenual fistula might

result, which in itself which in itself may cause gallstone ileus following dislodgement of gallstones into the intestine (127).

2.3 CHOLECYSTECTOMY

2.3.1 OPEN CHOLECYSTECTOMY

In 1882, Carl Langenbuch performed the first cholecystectomy on a 43-year-old male suffering from biliary colic in Berlin (128). Rates of primary open cholecystectomy (OC) have declined substantially since the introduction of LCC in 1985, with less than 10% of cholecystectomies started out as OC nowadays (8,79). Among indications for OC are severe inflammation, previous upper abdominal operations, cardiothoracic morbidity preventing the use of pneumoperitoneum, and septic shock. Yet, international guidelines recommend attempting LCC even for the elderly or severely ill after initial stabilization and optimization of preoperative conditions (69,95,101). Previously as well, Mirizzi syndrome was considered an absolute indication for primary OC, but recent case series have reported successful laparoscopic treatment of it among experienced surgeons (129).

To perform OC, the surgeon makes a right subcostal (Kocher's) incision. Traditionally, the surgeon mobilizes the fundus first and dissects down to the neck of the gallbladder to identify the hepatocystic triangle and to expose the cystic duct and artery. Alternatively, dissection can begin at the neck of the gallbladder in the same fashion as in LCC. The gallbladder may be decompressed with needle aspiration, if it is remarkably distended. The cystic duct followed by the cystic artery are clipped and divided. The gallbladder is detached from the gallbladder fossa and the fossa is inspected for bile leaks or bleeding. Drains indicating bile leak may be left in place should the surgeon be uncertain of the ligation of the cystic duct. The abdomen is closed in a standard multilayer fashion.

2.2.2 LAPAROSCOPIC CHOLECYSTECTOMY

Inspired by the vast use of laparoscopy in gynecological surgeries, Erich Mühe performed the first LCC in 1985 in Böblingen in Germany using a laparoscope of his own design called the "Galloscope" (130). The new technique initially received much skepticism but went on to gain worldwide popularity in the 1990s. Traditionally, LCC is performed with four ports, which can be placed in the American or the French way.

In the French way, the patient's legs are spread out as much as possible and the surgeon stands between the legs. An assistant holding the camera and the liver retractor stands on the left side of the patient. The camera port is placed supraumbilically, and the other ports are placed in midline epigastrium, in the right flank and in the left flank. In the American method, the surgeon stands on the left of the patient, with the assistant holding the camera on the left of the surgeon. The camera port is inserted supraumbilically

with two 5 mm ports placed laterally in the right flank. One 10-12 mm port is inserted midline in the epigastrium. When compared in ergonomy only, Kramp *et al.* found no difference between the two techniques (131). The techniques have not been compared in terms of patient outcomes.

Operating technique recommended by the Tokyo Guidelines and European Association of Endoscopic Surgery will be presented in the next section (26,132). Once the ports are placed, the gallbladder is lifted from its fundus to expose the neck of the gallbladder, and Hartmann's pouch is grasped. With traction, the hepatocystic triangle is exposed. The hepatocystic triangle is usually dissected with cautery. Ultrasound scissors may be used. When using cautery, the surgeon should cauterize small portions of tissue at a time. The effect should be small enough (max 30 W) and burning should take no longer than 1-2 seconds. The surgeon strives at achieving the Critical View of Safety (CVS) (further discussed in the following chapter) to safely confirm anatomy. Once CVS has been reached, the cystic artery and the cystic duct are ligated. The gallbladder is detached from the liver using cautery cautiously to minimize the risk of perforation. Gallstones falling into the abdominal cavity should be collected, as they might cause problem several years later; gallstones migrating through the diaphragm or the flank have been reported (133). If subvesical ducts are encountered, they should be cauterized or ligated. Alternatively intraoperative cholangiogram (IOC) may be used to see how substantial a portion of the liver they drain. The gallbladder is placed in a plastic bag and removed through the epigastric or umbilical port. The liverbed should be inspected for bleeders. Most bleeders can be managed with cautery or by compression, but a hemostatic pad may be left in place as well.

Routine prophylactic antibiotics in elective LCC did not show any statistically significant advantages in a meta-analysis on RCTs in 2010 (134). A more recent meta-analysis in 2018, however, showed that prophylactic antibiotics at induction of surgery significantly lowered the risk of postoperative infections (135). Gallbladder perforation during elective LCC is a risk factor for postoperative infection, yet administration of prophylactic antibiotics following perforation, has not lowered the infection rate (136,137). In acute cholecystitis, preoperative antibiotics are always recommended and they should be continued postoperatively in moderate to severe cholecystitis (101).

In his studies on the world's first 94 LCC patients, Mühe noted that his LCC patients had significantly less pain in their operating scars than OC patients even 5 years after surgery (130). The advantage of less pain postoperatively and thereby shorter hospital stays and lower health-care expenses with LCC has later been demonstrated by several randomized controlled trials (3-5). Therefore, following the introduction of LCC in 1985, the rates of cholecystectomy increased with up to 28% in the five following years (138), and with up to 90% in the following 20 years (139). Even though LCC was associated with lower mortality, the crude numbers of cholecystectomy-related deaths and complications have remained the same as

in the era of open cholecystectomy, as the rates of cholecystectomy have in themself increased (79,138).

In recent years, technology advances have led to the introduction of 3D LCC. In RCTs by Koppatz *et al.* and Schwabb *et al.,* 3D LCC did, however, not show any advantage compared with 2D LCC in regard to intra- or postoperative complications and operation time (140,141).

Initially, LCC was associated with a spike in BDIs (142). However, over the time, as surgeons have adjusted to the laparoscopic technique, the rate of severe BDI has fallen to 0.2-0.5% (13,14), closer to the 0.2% level of OC (143). BDI rates lower than those of OC have also been reported, as Halbert *et al.* reported a study on 155 000 patients who had undergone LCC in the New York state in 2005 to 2010, where only 0.08% required surgery for BDI (144), and O'Brien *et al.* reported an overall BDI rate of 0.08% on 1.2 million patients who received LCC in 2010-2018 (145). For avoiding BDIs, several surgical identification techniques are available.

2.3.2.1 THE CRITICAL VIEW OF SAFETY

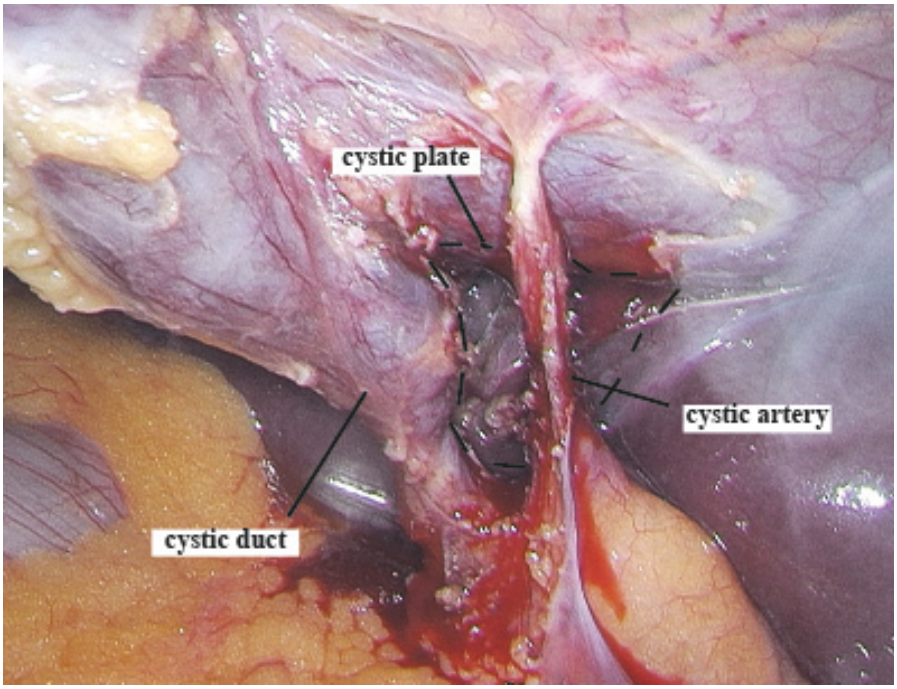

Figure 4 The Critical View of Safety. The hepatocystic triangle has been cleared, only 2 structures enter the gallbladder, and the lower third of the cystic plate is visible.

The Critical View of Safety (CVS) is a target identification technique that Strasberg *et al.* introduced in 1995 as means to tackle the increased BDI rate that came with the introduction of LCC and its difficulties in anatomical

identification (18). To obtain CVS, dissection is begun at the neck of the gallbladder and CVS is achieved when surgeon can see 1. the hepatocystic triangle free of fat and fibrous tissue, 2. two and only two ducts (the cystic duct and artery) entering the gallbladder, and 3. the lower third of the gallbladder lifted off the cystic plate. Following CVS achievement, the structures may be clipped and divided, and the gallbladder is detached from the liver.

International guidelines recommend CVS (26,132). The evidence on the superiority of CVS as a ductal identification technique is not strong. CVS recommendations are based on observational studies, where the BDI rate has been lower than expected (19,20,146). Regardless, these observations are based on operative notes. When intraoperative videos or photos have been analyzed, experts have concluded that CVS has been rightfully achieved in 10-20% of LCCs (15,22). Similarly, however, in these photo or video evaluation studies, achieved CVS has not been associated with any BDIs (15,21-23).

2.3.2.2 OTHER DUCTAL IDENTIFICATION TECHNIQUES

The infundibular technique is based on identifying the funnel shaped appearance of the junction of the gallbladder and the cystic duct (147). Under easy conditions, it is fast and feasible. However, the error trap in the infundibular technique arises in situations with alternative anatomy, such as a short cystic duct or fusage of the cystic duct to the CBD or entrapment of a large stone or traction difficulties (148,149).

In the “fundus first”, “dome down” or “antegrade” technique, dissection begins at the fundus of the gallbladder all the way down to the neck of the gallbladder (147). It is, however, noted to be hard to manage laparoscopically due to loss of cephalic traction. Furthermore, it has been associated with ‘extreme’ vascular injuries, in cases of severe inflammation and cystic plate contraction, where dissection has inadvertently been carried on into the liver hilus (150). Hence, guidelines do not recommended the fundus first technique as a bail-out strategy (132).

2.3.2.3 INTAOPERATIVE CHOLANGIOGRAPHY

Intraoperative cholangiography (IOC) decreases the risk of bile duct injuries by confirming the anatomy intraoperatively. However, interpreting cholangiograms requires expertise as some studies have reported rates as low as 6-30% of correct IOC interpretation, with wrongful interpretations sometimes leading to BDI (151-153). Furthermore, BDIs occurring during IOC catheter insertion have been reported as well (151). Some studies recommend the use of cholangiography routinely as it lowers the risk of BDI and postoperative mortality (154,155). According to a Swedish meta-analysis, the use of routine IOC seemed cost-effective as it reduced the economic burden of treating BDI (156). Guidelines do not recommend the use of IOC routinely, but reserve it for cases when anatomy is unclear or when BDI is suspected, as even untrained residents have reached a sensitivity of >90% in identifying abnormal anatomy (major BDI or bile duct stones) (132,157,158).

2.3.2.4 INDOCYANINCE GREEN FLUOROSCOPY

In recent years, intraoperative indocyanine green (ICG) fluoroscopy has emerged as an identification method. ICG is injected intravenously one hour before surgery, metabolized by the liver, and secreted into bile. Intraoperatively, an endoscopic fluorescence imaging system distinguishes the ICG containing bile ducts from surrounding tissues. In a randomized controlled trial comparing LCCs with ICG to LCCs without ICG, ICG was superior in detecting the location of biliary structures prior to dissection (159). A case-control study comparing ICG with IOC reported similar abilities in bile duct identification, yet shorter operating times with the use of ICG (160).

2.3.3 CONVERSION

In conversion, a laparoscopically started cholecystectomy is converted to laparotomy. There are no generally accepted criteria for when an LCC should be converted, but the 2020 World Society of Emergency Surgery Guidelines recommend conversion in case of severe inflammation, adhesions, bleeding or suspected BDI (86).

Overall a rate of 1-6% conversion is reported in elective LCC and 6-18% in LCC for acute cholecystitis, but the rates vary severely in response to different surgical conditions (7,8,10-12). In gangrenous cholecystitis, conversion rates of up to 30-50% have been reported (96,161).

As mentioned, severe inflammation is a strong risk factor of conversion (161). Other identified risk factors are age, diabetes, BMI, male sex and previous upper abdominal surgery. (10,11,162,163).

Conversion is initiated in a similar fashion as OC. The trocars are removed, and the abdomen is entered through Kocher's incision. As with OC, conversion is related to a longer hospital-stay and more wound complications.

2.3.4 SUBTOTAL CHOLECYSTECTOMY

In cases of unclear anatomy caused by severe inflammation or adhesions, among others, the surgeon might opt for subtotal cholecystectomy and remove only a portion of the gallbladder with structures like Hartmann's pouch and the cystic duct left intact. Subtotal cholecystectomy aims at minimizing the risk of BDI when the anatomy is unclear. Subtotal cholecystectomy was first introduced in OC in 1985 by surgeons Bornman and Terblance (164), and performed laparoscopically in 1993 for the first time (165).

Meta-analyses have concluded that correctly performed subtotal cholecystectomy is as good as regular cholecystectomy in terms of bile leaks, BDIs and postoperative complications (166,167). However, literature remains divided on what constitutes subtotal cholecystectomy, as some argue only LCCs, where the cystic duct is not identified and clipped, should be named subtotal cholecystectomy (168). The cystic duct may be clipped or closed from within Hartmann's pouch, with a strip of posterior gallbladder mucosa adhering to the liver. In these cases, the cystic duct is identified, and the rate

of bile leaks and postoperative complications has been reported similar to that following regular LCC in studies homogenous for cystic duct ligation (168-170). If the cystic duct cannot be identified, Hartmann's pouch is left open and drained, or stapled or sutured shut. A drain should be left in place as an indicator of bile leak. This approach is associated with a significant increase of bile leaks as opposed to LCCs where the cystic duct is clipped (168). However, around 25% of these bile leaks resolved on their own without the need for ERC. The meta-analyses indicating subtotal cholecystectomy as favorable as regular LCC have been heterogenous for all techniques defined as subtotal cholecystectomy, and might hence be biased on the feasibility of subtotal cholecystectomy.

2.3.5 POSTOPERATIVE COMPLICATIONS

As with all procedures, LCC carries a risk of complications. Generally, studies have reported overall postoperative complication rates 2-10% of for LCC (14), with 11% for emergency LCC and 6% for elective LCC (13,79,171). The complication rate as well is subject to reporting and classification of complications. Complications can be classified into surgical and anesthesiologic complications and furthermore into intraoperative and postoperative complications.

Studies on risk factors for complications have recognized age and male sex as risk factors for complications (172,173). Patients with renal impairment have a higher risk of complications (172). Sepsis, emergency LCC or conversion have further been identified as risk factors for postoperative complications (7,172,174). Especially the risk of surgical site infections and wound complications is higher in acute cholecystitis than in elective procedures due to the bacterial contamination of the tissues. Severe inflammation is a serious risk factor, as Ausania *et al.* reported a morbidity rate of 57.7% and a mortality rate of 9.5% in patients with perforated acute cholecystitis (175).

The overall mortality after LCC is low at only 0.1-0.7% (13,176,177). Surgical mortality has been found to be higher in older patients operated on for acute cholecystitis with more comorbidities who required conversion to open cholecystectomy (173,176,177).

The risk of intraoperative or postoperative bleeding requiring blood transfusions has been reported at 1-2%, with a 0.1% mortality rate (178-180).

2.3.6 BILE DUCT INJURIES

Even though BDI is a rare event, LCC is performed in such high numbers worldwide that BDIs constitute a substantial part of iatrogenic harm caused to patients and costs in health-care related expenses. Moreover, with the introduction of LCC for symptomatic gallstone disease, the criteria for surgery have loosened compared with the era of open cholecystectomy (138,139,181).

In worst case scenarios, a young previously healthy individual undergoes LCC for mild symptoms and ends up with a lethal complication, or a completely severed CBD requiring years of follow-up, endoscopic procedures and eventually end-stage liver disease requiring liver transplantation.

With 9000 LCCs annually performed in Finland, around 30 patients each year suffer a major BDI taken an 0.3% incidence rate as reported in Study III. Even though the management of BDIs nowadays is well-developed and patients' QoL in long-term is as good as of those having received an uneventful LCC, patients with BDI still require extensive follow-up and might require yearly interventions for strictures, and liver transplantation should the stricture result in end-stage liver disease (145,182,183). Even with extensive use of CVS and bail-out techniques, the risk of BDI will hardly ever be completely eliminated, but BDIs that could have been prevented with thorough identification techniques should not happen.

2.3.6.1 CLASSIFICATION AND DIAGNOSIS OF BILE DUCT INJURIES

Bile duct injuries (BDIs) are reported in various ways, leading to difficulties establishing an accepted rate of BDI following LCC. Reported overall BDI rates including bile leaks have been reported at 0.7-1.7% (17) with major BDI rates from 0.2% to 0.5% (13-17). Kum *et al.* reported a CBD injury rate of 5.5% for acute cholecystitis and 0.2% for elective LCC (12). According to literature, BDIs are usually classified as mild or major. Major BDIs usually constitute injuries to major bile ducts, but some literature reports only BDIs requiring reoperations excluding BDIs managed in the primary operation or endoscopically. Several classification systems for bile duct injuries have been suggested. The Strasberg classification accounts for all types of injuries regardless of required treatment and is the most frequently used BDI classification. It is presented in Table 2 and Figure 5 (18,184).

TABLE 2. Bile duct injuries according to the Strasberg classification

TYPE	DEFINITION
Class A	Bile leak from cystic duct or liver bed without injury to continuity
Class B	Partial occlusion of the biliary tree, usually from an accessory right hepatic duct
Class C	Bile leak from duct (right aberrant hepatic duct) that is not communicating with the common bile duct
Class D	Lateral injury of the biliary system, without loss of continuity
Class E	Circumferential injury of the biliary tree with loss of continuity
E1	CBD stricture > 2 cm distal to hepatic confluence
E2	CBD stricture < 2 cm distal to hepatic confluence
E3	Hilar stricture without residual CBD, but intact confluence
E4	Destruction of hepatic confluence
E5	Stricture involving right accessory duct and CBD

CBD Common bile duct

The Class E (Table 2, Figure 5) can further be subcategorized into E1-E5 depending on how high from the liver confluence the bile ducts have been cut.

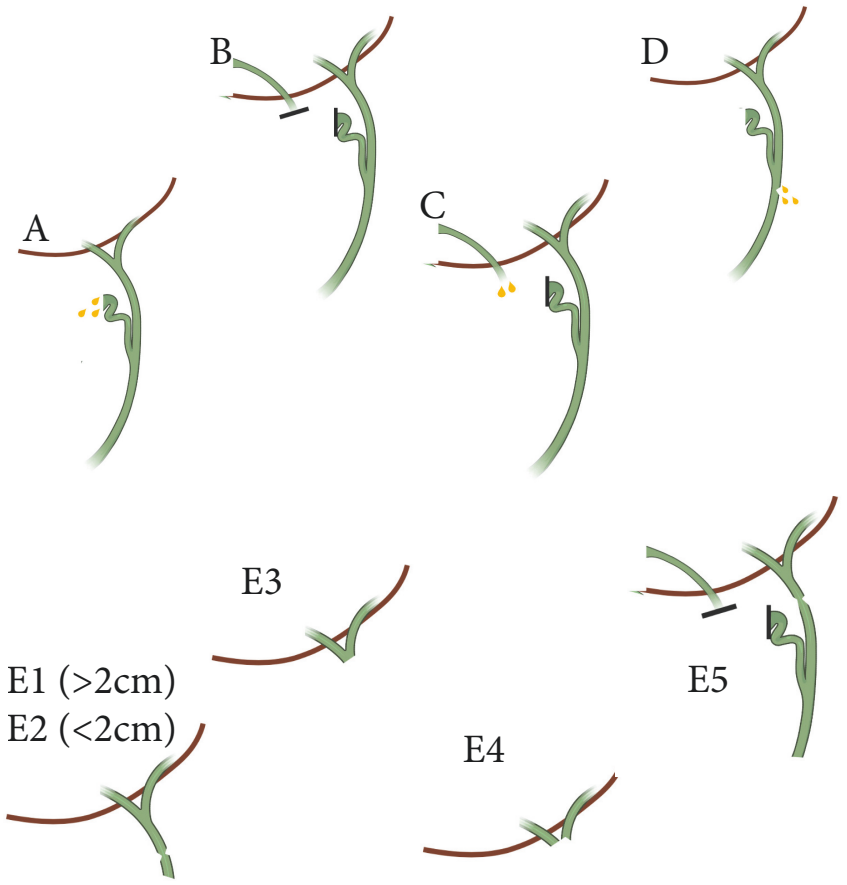

Figure 5 The Strasberg classification of bile duct injuries

BDIs present principally in two ways; intra-abdominal bile leaking causing pain and secondary biliary peritonitis (or biliary drain output taken a drain was left in place) or biliary obstruction causing pain and jaundice (185). Retroperitoneal bile leaks presenting with similar symptoms as intra-abdominal bile leaks have been reported (186). BDIs may be recognized due to macroscopic appearances or IOC intra-operatively. Postoperatively, MRCP and ERC are useful tools in recognizing BDIs (185).

VASCULOBILIARY INJURY

Vascular injury usually affects the right hepatic artery (RHA). Injury to the RHA has been present in 27-60% of severe bile duct injuries (148,187). The effect of accidental ligation of the RHA on the liver's function seems individually different. Patients with incidentally ligated RHAs discovered in autopsies have shown no recorded postoperative complications or raised liver morbidity following their cholecystectomy (188). Nevertheless, in case reports, RHA ligation has resulted in severe liver ischemia requiring liver transplantation (189).

2.3.6.2 MECHANISMS OF BILE DUCT INJURY

BDIs occur for various reasons. In the introduction of LCC, BDIs were attributed to the learning curve of LCC (142). Now, with over 30 years since the introduction of LCC, BDIs can no longer be attributable to surgeons trying to perfect or find the right technique for the procedure. Injuries sustained from LCC have not significantly differed from those occurring during OC (190). Acute cholecystitis has been noted as a risk factor of BDI, as it makes the anatomy harder to read and the tissues harder to dissect due to adhesions (12,17,191). Especially Class A injuries occur frequently after acute cholecystitis as the inflamed tissues may be too frail to close. Class A injuries are rarely related to surgeon's inexperience but rather to the underlying conditions. Class D injuries might also be attributed to difficult conditions, following chronic cholecystitis when the CBD and Calot's triangle are scarred from fibrous tissue and adhesions. Similarly bleeding or poor visibility might attribute to partial severing of the CBD (Class D) (148). BDIs might also occur during IOC if the CBD is cut when trying to make the incision for the catheter in the cystic duct (148).

Misidentification of anatomy is a common source of Class B, C and E injuries (148,191). In type B injuries, the accessory duct might be mistaken for the cystic duct or a blood vessel. In type C injuries, the accessory duct is usually not noted at all, and is cauterized while dissecting the cystic plate. In the severest form of BDI - class E injuries - usually the whole CBD or the right hepatic duct is mistaken for the cystic duct leading to its complete transection (142,148). Class E injuries may also occur in response to careless use of cautery, or accidental placement of clips when trying to control for bleeding (148). Injuries to the right hepatic duct have been attributable to misidentification of the RHD as the cystic duct in 64% and due to accidental lateral injury during dissection with a low-lying RHD (148).

Anatomical variations clearly heighten the risk of BDI (191). In some cases, injury to the bile ducts is inevitable. In the instance of accessory bile ducts connecting to the gallbladder and draining parts of the liver, the surgeon must decide on whether to ligate the duct or attempt anastomosis to the common bile duct. In the rare cases of complete agenesis of the cystic duct and the gallbladder attached directly between the common hepatic and the common bile duct, the only choice is to attempt a primary

hepaticojejunostomy (30). Even though these cases are extremely rare occurring in 1 of 2000 patients, GI surgeons are likely to encounter them during their career.

The risk of class E injury in relation to the surgeon's experience remains somewhat unclear. GI surgeons usually encounter only 1-2 to class E injuries throughout their career, and in surveys, most surgeons have reported their BDIs after around 100 to 200 cases, perhaps due to a false sense of mastering the procedure (192). Similarly young drivers seem to have highest risk of accidents around six months after getting their driver's license due to overconfidence in their abilities (193).

2.3.6.3 TREATMENT OF BILE DUCT INJURIES

The treatment of BDI depends on the class of BDI, the mechanism of injury and how soon they are noticed. In a study on 252 Class D-E BDIs, 75% were recognized intraoperatively (148). In CBD injuries noticed only postoperatively, the CBD was clipped as the cystic duct, and when the cystic duct was encountered during freeing the gallbladder from the liver, it was attributed as an accessory duct (148,191).

Strasberg A – Class A injuries usually present postoperatively and are mostly treated endoscopically through ERC, sphincterotomy with or without stent insertion to decrease intraductal pressure (185,194). Intra-abdominal bile collections should be drained percutaneously.

Strasberg B – Class B injuries presenting with mild symptoms such as transpiring pain and light elevation in liver function tests may be treated conservatively. Development of cholangitis requires administration of antibiotics and percutaneous drainage of the occluded liver segment if the patient does not respond to antibiotics alone. If the accessory duct drains major parts of the liver, hepaticojejunostomy may be needed (185,195) .

Strasberg C – Class C injuries usually result in bile leak from an accessory duct as the draining stump is not occluded. Subhepatic bile collections may form and progress to biliary peritonitis and septic shock. Some bile leaks resolve spontaneously whilst continuous bile leaks usually require percutaneous drainage and sometimes hepatectomy. Hepaticojejunostomy may be needed (185,195).

Strasberg D – If noticed intraoperatively, a small enough defect may be sutured with absorbable monofilament suture. A drain should be left as an indicator and ERC in combination with stenting should be done with low threshold (185).

Strasberg E – Class E injuries always require surgical treatment. The primary treatment should be hepaticojejunostomy performed by a hepatopancreaticobiliary surgeon (182,183,185,196). Primary end-to-end anastomoses are not recommended as they are highly prone to strictures (197). Should the patient develop biliary peritonitis, it is recommended that the operation be postponed until the patient has stabilized (182,197). In a meta-analysis on optimal time for BDI treatment, patients who received

hepaticojejunostomy between 2 and 6 weeks from injury had the highest risk of morbidity and stricture formation (198). In high bile duct injuries with no viable ducts to use for hepaticojejunostomy, the jejunal loop must be sutured to the liver parenchyma similarly to the Kasai portoenterostomy (199,200).

Even initially successfully managed BDIs might develop strictures in the bile duct leading to liver disease. Transplantation has been performed several years after the initial injury, due to strictures, persisting cholangitis and the development of end-stage liver disease (182,183). In addition, in single case reports, clipping of the right hepatic artery or the portal vein eventually resulting in liver failure has been treated successfully with liver transplantation (189,201).

2.3.6.4 QUALITY OF LIFE AFTER BILE DUCT INJURIES

The outcome of BDI repair is related to the type of injury. In minor injuries (type A) treated successfully primarily no strictures or increased mortality has been noticed (185). Furthermore, in injuries managed endoscopically, the quality of life remains largely unaffected in the long term. During the first year, however, the patient might need to undergo several ERC procedures for stent change or stent removal.

The most significant decrease in quality of life can be observed in patients requiring hepaticojejunostomy. The bile duct anastomosis is suspectable to strictures, which at worst lead to liver cirrhosis requiring liver transplantation (182,183). Schreuder *et al.* found that strictures occurred at a median time of 11 to 30 months following injury (196). Therefore, patients treated successfully for BDI need long-term follow-up to detect strictures.

In a questionnaire study on quality of life (QoL) by Koppatz *et al.*, patients treated for major BDI (Strasberg E) did not have lower scores in QoL compared with controls of patients who had undergone LCC without BDI (183). However, a retrospective analysis by Flum *et al.,* found that patients who had suffered injury to the CBD, had a three-times higher risk of dying compared with patients with an intact CBD (202). Similarly, Fong *et al.* reported increased mortality at 1-year for patients with bile leak (OR 1.85, $p<0.001$), and with BDI (OR 2.04, $p<0.001$) (16). Even more extreme, death following BDI and associated vascular injury and liver ischemia has been reported (150).

2.4 LEARNING LAPAROSCOPIC CHOLECYSTECTOMY

2.4.1 SURGICAL EDUCATION IN FINLAND

Surgical education in Finland has undergone many changes in the recent decades. The five universities with medical faculties in Finland (Helsinki, Turku, Tampere, Oulu, Kuopio) are responsible for the surgical education in Finland. Until 1998, physicians specialised first to become specialists in general surgery, after which they could choose the more narrow subspecialty of gastrointestinal surgery. Following 1998, a two year and three months period in a district hospital called the "common surgical trunk" was required. The last three years were spent at a university hospital within the chosen specialty (203). Beginning in 2020, the surgical education underwent its most recent change. Currently, applicants are chosen to specialize by each of the five universities in Finland. Applicants are ranked according to previous work experience, scientific merits, and interview skills. A 9-month primary health care period is required where the future surgeons familiarizes themselves with common diseases and makes an understanding of the Finnish healthcare system. The university has provided guidelines of what procedures should be handled, but there are no certain amounts of surgeries specified that the resident needs to perform before graduating as a specialist in GI surgery. The resident undertakes the residential board exam and a specialist written exam at the end of the specialization program. After graduating as a specialist in GI surgery, the surgeons may undergo further subspecialisation. This is usually done at a university hospital by working within the chosen specialty. Surgeons working at district hospitals usually handle a broader range of procedures from upper to lower GI procedures compared with GI surgeons in university hospitals who focus on a narrower field.

The work week of surgical education in Finland has changed as well in the last decades – previously weekly working hours were under no restrictions, whilst starting from 2020, weekly working hours should be limited to a maximum of 48 hours. In comparison, surgical residents in the USA work an average of 80h/week resulting in 19,200 hours average total time of training for 5 years (204). 3963 hours (16.5 h/wk) was spent on operative training in the USA. Worldwide, however, surgical training programs exhibit significant variation; weekly working hours vary from 38h to limitless, the length of training varies from 4 to 10 years, and some countries require a minimum number of surgeries (205).

Surgery requires many specific skills. In terms of surgical technique, the surgeon needs to acquire both good motor skills along with knowledge of treatment options in a sometimes-high-pressured environment. The next sections will mainly focus on learning and maintaining operating technique.

It remains a question, whether expert surgical skill is a result from inherited excellency in general motor skills and visuospatial ability or acquired through practice. Surgeons' personality and leadership styles have been

associated with complication rates as well (206). The pioneering studies of psychologist Ericsson *et al.* on pianists laid the ground for the now widely accepted theory that expert skill is acquired through "deliberate practice" rather than inherited abilities (207). The study of Ericsson *et al.* compared amateur pianists with expert pianists, who had acquired significantly more training hours than the amateur pianists. Expert pianists performed significantly better than amateur pianists in all tests measuring piano skill, but in general tests on perceptuous motor speed, cognitive-motor speed and simple motor efficiency, no statistically significant difference between the groups emerged. It cannot be generalized that operating technique is learnt in a similar fashion as playing the piano is, but the studies by Ericsson *et al.* demonstrate the ability of becoming an expert in an art requiring fine-motor skills and hand-eye-coordination through meticulous practice rather than inherited motor skills. Similar studies on for example expert consultants and junior resident surgeons have, however, not been conducted.

However, Ericsson et *al.,* stress that instead of mindless repetitions, practice needs to be "deliberate" systematic practice with the goal of improving performance. They speculate that experts are those who continue to develop throughout their whole career instead of remaining at a plateau of acquired expertise.

What makes surgical learning unique, is the "master-apprentice" type of fashion in learning. This places immense weight on the teachers since as demonstrated by a study on residents in radiology whose diagnostic accuracy approached the diagnostic accuracy of their teachers without ever exceeding it (208). Nevertheless, residents are influenced by several teachers whom they can take influences from, and finally become more skilled than their teachers alone.

Surgical simulators have been tested to enhance surgical performance. Training on surgical simulators such as laparoscopy box and virtual reality simulators have translated into greater skill in the actual procedure for residents with limited laparoscopic experience (209,210).

2.4.2 OPERATING VOLUME IN LAPAROSCOPIC CHOLECYSTECTOMY

The effect of volume and surgeon's specialization has been well-documented, favoring high-volume hospitals and specialized surgeons as stated by a systematic review on articles published between 1957 and 2007 examining volume outcome in surgery (211). A study examining the correlation of surrogate operations (operations similar to the index operation) on the outcome of esophagectomy found that surgeons who performed high volumes of surrogate operations similarly had lower mortality rates for the index operation as well (212). This clear linear association of volume and better surgical outcome, has to lead to the centralization of procedures with low annual volume, such as pancreaticoduodenectomies to the five university hospitals in Finland (213,214). Similarly to studies on any surgery, heterogenous studies on LCC have shown subspecialized surgeons with high

annual and cumulative volumes have had the lowest conversion and readmission rates, and shortest postoperative stay (215-218). However, studies on LCC for heterogenous indications have demonstrated no correlation between surgeons' cumulative or annual volume and postoperative complications (219,220). In studies on LCC for acute cholecystitis, surgeons with annual high volume had lower conversion rates and shorter postoperative stays (221). Kortram *et al.* found that laparoscopy-oriented surgeons (>50 laparoscopies/year) had significantly lower conversion rates for acute cholecystitis (3.6% vs 15.6%, p=0.003) (222). In a study on risk factors for complications, Giger found that cumulative volume under 100 LCCs had a higher risk of complications (OR=1.36; p<0.0002) (7).

LCC is still carried out at all 16 community district hospitals and 5 university hospitals in Finland, leading to an average number of 400 LCCs / year / hospital. However, on the one hand, specialized centralized care might yield better outcomes, but on the other hand, centralizing procedures might lead to restrictions in surgical training and challenges in providing high-quality local care emergently. Naturally, a guideline recommending only highly specialized surgeons to conduct cholecystectomies cannot be given.

3 AIMS OF THE RESEARCH

I To identify risk factors for conversion and postoperative complications in patients receiving LCC for acute cholecystitis (STUDY I)

II To evaluate the association of the surgeons' previous experience and annual volume with conversion and postoperative complications in LCC for acute cholecystitis (STUDY II)

III To evaluate the association of photo documentation of CVS with BDIs in LCC (STUDY III)

IV To identify user trends in CVS among individual surgeons (STUDY IV)

4 PATIENTS AND METHODS

4.1 STUDY HOSPITALS

Study I and II took place in Meilahti Hospital from 2013 to 2016, whilst Study III and IV took place in both Meilahti and Jorvi Hospitals in 2018 to 2019. Both hospitals are part of Helsinki University Hospital, which serves as a secondary referral center for 1.2 million and tertiary referral center for 1.9 million inhabitants.

4.2 STUDY DESIGN

Study I and II were retrospective studies, and patient data regarding characteristics, the operation, surgeons, and outcomes were collected retrospectively from electronic medical records.

Study III and IV were prospective studies with intraoperatively collected photos. Surgeons were instructed to take one anterior and one posterior photo of the view before placing clips on the alleged cystic duct and artery. Halfway through the study, a lecture on safe LCC and CVS was, and surgeons were encouraged to use and record CVS from there on. Before the lecture, 46 surgeons anonymously completed a questionnaire on their experience in LCC and knowledge of CVS.

4.3 PATIENTS

Study I. A total of 499 patients treated from January 2013 to December 2014 were identified from the operating room database with procedure codes JKA20 and JKA21 for cholecystectomy and ICD codes K80.0, K80.4, K81.0 for acute cholecystitis. Fifty-four patients were excluded due to acalculous cholecystitis, and 33 due to missing signs of acute inflammation on the gallbladder. Nine excluded patients received cholecystectomy during the treatment of another disease that required hospital care and three patients were excluded due to gallbladder malignancy. Twenty-seven patients with primary open cholecystectomy were excluded. The remaining 373 patients with acute calculous cholecystitis were included into analysis.

Study II. Study II included the patient population of Study I, with the addition of patients with acalculous cholecystitis in 2013 to 2014 and patients treated from January 2015 to December 2016. Patients were identified with procedure codes JKA20 and JKA21 for cholecystectomy and ICD codes K80.0, K80.4, K81.0 for acute cholecystitis. Of the 1062 patients identified patients, 71 patients were excluded due to a primary open approach. Furthermore, 72

patients were excluded due to lacking signs of acute inflammation on the gallbladder intraoperatively, and 27 patients had already been admitted to hospital and received treatment for another disease prior to cholecystectomy. These exclusion criteria yielded 892 patients for the final analysis.

Study III. Patients treated in Meilahti Hospital from April 2018 to October 2019 and in Jorvi Hospital from October 2018 to October 2019 were retrospectively identified from the operating room database using procedure codes (JKA21 and JKA20) and ICD codes for benign gallbladder disease (K80.0-K85.9). The electronic records of 1683 patients were extracted. Forty-six primarily open cholecystectomy patients were excluded. Furthermore, 89 patients, whose surgeries were converted prior to dissection of the cystic duct and artery, were excluded. Moreover, five patients had cholecystectomy in addition to another surgery and were excluded. One patient lacked the operation note and was excluded. These exclusion criteria yielded 1532 patients for final analysis.

Study IV. Study IV included the same 1532 patients as study III, with the addition of a subanalysis including 89 patients who received converted emergency LCC.

4.4 SURGEONS

Residents were completing their surgical residency with rotations in different subspecialities at Helsinki University Hospital. Most residents had undergone at least 2.5 years of residency at a community hospital and were specializing in GI surgery, but a minority were specializing in vascular surgery or urology. GI surgery consultants were focusing on different subspecialities during daily working hours (upper GI, lower GI, endoscopy, bariatric surgery, emergency abdominal surgery).

4.5 DEFINITIONS

Postoperative complications were rated according to the Clavien-Dindo Classification of Surgical Complications (223) as presented in Table 3. The Comprehensive Complications Index was calculated for each patient (224).

TABLE 3. CLAVIEN-DINDO CLASSIFICATION OF SURGICAL COMPLICATIONS

GRADE		DEFINITION
I		Deviation from normal postoperative course treated with: antiemetics, antipyretics, analgesics, diuretics, electrolytes or physiotherapy. Wound infections opened bedside.
II		Pharmacological treatment with other drugs than grade I complications. Blood transfusions and total parenteral nutrition.
III		Requiring surgical, endoscopic or radiological intervention
	a)	Intervention without general anesthesia
	b)	Intervention under general anesthesia
IV		Life-threatening complication requiring IC/ICU-management
	a)	Single organ dysfunction (including dialysis)
	b)	Multiorgan dysfunction
V		Death

IC Intermediate care ICU Intensive care unit.

BDIs were rated according to the Strasberg classification (18). **Physical status** was assessed with the American Society of Anesthesiologists (ASA) classification given by the anesthesiologist in charge. **Operating time** was defined from initial incision to wound closure. **Acute cholecystitis** was defined as macroscopic or microscopic signs of acute inflammation on the removed gallbladder.

In Study II, **high-volume surgeons** were defined as surgeons with more than 5 LCCs for acute cholecystitis annually (average 2013-2016), and **low-volume surgeons** as surgeons with 5 or fewer LCCs for acute cholecystitis annually (average 2013-2016). **Lead surgeon** and **assistant** were determined according to the operating note.

In Study III, **satisfactory CVS** was defined as photos receiving a rating of 4.5 or higher. Four consultant GI surgeons rated the photos. They were blinded to all patient data and received photos randomly. Two raters independently scored both the anterior and posterior photos of each patient. Each three criteria (excess fat cleared off Calot's triangle, only two structures enter the gallbladder, gallbladder lifted of the lower third of the cystic plate) of CVS received scores of 0 to 2 according to Sanford *et al.* (225). The doublet score from 0 to 6 was the sum of the better scored criteria for CVS. For example, if the anterior photo scored 2 points on only 1/3 criteria of CVS, but the posterior photo received 2 points on each remaining 2/3 criteria, the doublet score would be 6 points. The final CVS score was the mean of the doublet scores of the two raters.

4.6 SURGICAL METHODS

In all studies, patients were treated according to the operating surgeon's preference. The American technique of trocar placement was used exclusively in LCC. Four ports were usually used, but in some cases a fifth port was inserted. OC was performed with Kocher's incision in the preoperative diagnosis of acute cholecystitis, and through midline incision if the preoperative diagnosis required it. Instruments for dissection were up to surgeon's preference, but usually electrocautery, blunt dissection with suction, or Harmonic scalpel was used. Surgeons used the identification technique they preferred. Following the middle of Study III, in March 2019, surgeons were actively encouraged to use the CVS method. IOC was available but not used routinely. ICG was not available.

4.7 STATISTICAL ANALYSIS

Analyses were performed with SPSS in all studies, with the addition of STATA in Study III and IV. In all studies, values were presented as means with standard deviation or medians with interquartile range. Normality for variables was tested using the Shapiro Wilks test. Non-normally distributed continuous variables were evaluated with the Mann-Whitney U, Kruskall-Wallis H or Jonckheere-Terpstra test. Pearson's or the Linear-by-Linear $\chi 2$ test was used for testing between categorical variables. Interrater agreement was assessed with the kappa statistic for categorical variables and the weighted kappa statistics for scale variables (0-6). For multivariate risk factor analyses a binary stepwise forward regression model was used. For calculating predicted probability, a multivariate regression model including all possible confounding factors was used. Case-mix adjusted outcomes were obtained with the formula (expected event rate / observed event rate x institution's average event rate). All p-values were based on two-tailed tests and the limit for statistical significance was set at 0.05. Funnel plots were drawn with GraphPad Prism and their confidence intervals were obtained with the method of normal approximation (226).

4.8 ETHICAL APPROVAL AND STUDY PERMISSION

The Institutional Review Board approved all study protocols. All studies were observational studies on patient files, and therefore Ethics Committee approval was not sought.

5 RESULTS

TABLE 4. PATIENT CHARACTERISTICS OF STUDY I-IV.

	STUDY I 2013-2014 n (%)	**STUDY II** 2013-2016 n (%)	**STUDY III** 2018-2019 n (%)	**STUDY IV** 2018-2019 n (%)
Number of patients	373	892	1532	1621
Indication for LCC	Acute calculous cholecystitis	Acute cholecystitis	All biliary complications	All biliary complications
Hospital	Meilahti	Meilahti	Jorvi & Meilahti	Jorvi & Meilahti
CHARACTERISTICS				
Sex; male	189 (50.7)	467 (52.4)	572 (37.3)	631 (38.9)
Age, median (range)	63 (20-94)	64 (18-96)	56 (16-97)	57 (16-97)
Diabetes	68 (18.2)	163 (18.3)	143 (9.3)	161 (9.9)
ASA score > 2	214 (57.4)	514 (57.6)	535 (34.9)	597 (36.8)
ACUTE CHOLECYSITIS	**n=373**	**n=892**	**n=549**	**n=633**
CRP, median (IQR)	145 (66-244)	148 (69-250)	140 (61-237)	150 (66-243)
WBCC, median (IQR)	13 (10-17)	13 (10-17)	13 (10-17)	13 (10-17)
Gangrene	135 (36.2)	328 (36.8)	162 (29.5)	206 (32.5)
Abscess	15 (4.0)	32 (3.6)	14 (2.6)	20 (3.2)
Perforation	36 (9.7)	87 (9.8)	24 (4.4)	40 (6.3)
OUTCOMES (ALL PATIENTS)				
Conversion	84 (22.5)	161 (18.0)	*	97 (6.0)
Postoperative complications	67 (18.0)	190 (21.3)	117 (7.6)	143 (8.8)
Operating time, median (IQR)	100 (76-125)	99 (75-127)	77 (59-105)	84 (65-115)
BDI	4 (1.1)	20 (2.2)	17 (1.1)	21 (1.3)

* Converted patients excluded

ASA American Society of Anesthesiologists BDI Bile duct injury CRP C-reactive protein IQR Interquartile range LCC Laparoscopic cholecystectomy

5.1 STUDY I

5.1.1 PATIENT CHARACTERISTICS

Table 4 shows patient characteristics of the 373 patients with acute cholecystitis included for final analysis.

5.1.2 RISK FACTORS FOR CONVERSION

Of 373 patients, 84 (22.5%) had conversion to open surgery. Patients with converted surgeries has significantly more complications compared with patients, whose surgeries were finished laparoscopically (29.8% *vs.* 14.5%, p<0.001). Univariate analysis identified age, diabetes, symptoms duration under 24h prior to admission, CRP, WBCC, gangrene and abscess as risk factors for conversion. Multivariable analysis identified CRP over 150mg/l, diabetes, age over 65 years, gangrene, and abscess as risk factors for conversion (Table 5).

5.1.3 RISK FACTORS FOR POSTOPERATIVE COMPLICATIONS

Altogether, 67 (18.0%) patients had postoperative complications. Univariate analysis identified male sex, age, impaired renal function, diabetes, previous laparotomy on the upper abdomen, CRP, and conversion as risk factors for postoperative complications. Multivariable analysis identified male sex, age over 65 years, impaired renal function, and conversion as risk factors for postoperative complications (Table 5).

TABLE 5. MULTIVARIABLE ANALYSES IN STUDY I

CONVERSION		
Preoperative risk factors*	OR (95% CI)	P
Diabetes	1.8 (1.0-3.3)	**<0.001**
CRP > 150mg/l	3.0 (1.8-5.0)	**0.045**
Both preoperative and intraoperative risk factors**		
Age > 65 years	1.9 (1.1-3.3)	**0.023**
Gangrene	5.9 (3.4-10.2)	**<0.001**
Abscess	9.2 (2.7-31.1)	**<0.001**
POSTOPERATIVE COMPLICATIONS***		
Age > 65 years	2.1 (1.2-3.6)	**0.012**
Male sex	2.1 (1.2-3.7)	**0.013**
Impaired renal function	4.8 (1.4-17.0)	**0.015**
Conversion	2.2 (1.3-4.1)	**0.006**

All models were obtained with stepwise forward regression models.
CI Confidence interval CRP C-reactive protein OR Odds ratio WBCC White blood cell count
* Age > 65 years, previous laparotomy on the upper abdomen, diabetes, CRP > 150 mg/l and WBCC > $13x10^9$/l were included into analysis.
**Gangrene of the gallbladder and abscess were added for the stepwise analysis of all risk factors.
*** Age > 65 years, sex, CRP > 150 mg/l, diabetes, impaired renal function, previous laparotomy on the upper abdomen, operating time > 90 minutes and conversion were included.
.

5.2 STUDY II

5.2.1 PATIENT AND SURGEON CHARACTERISTICS

Table 4 shows patient characteristics of the 892 patients with acute cholecystitis included for final analysis. Altogether, 76 surgeons performed 892 LCCs as lead surgeons over the four-year period, resulting in an average of 2.9 procedures a year. Of the lead surgeons, 39 were residents, 24 were consultants, and 13 surgeons operated both as residents and consultants (i.e., graduated during the study period). Additionally, 11 consultants acted only as assistants to residents. Residents started out as lead surgeons in 558 (62.6%) LCCs, and they were assisted by a consultant in 242 (27.1%) of the procedures.

The surgeons' mean age was 40 (in 2013), and 53 (60.9%) of them were women. Of the consultants, all were specialized in GI surgery, but during daily working hours, 16 (33.3%) were concentrating on general surgery, 11 (22.9%) on colorectal, six (12.5%) on upper-GI (including hepatopancreaticobiliary surgeons), five (10.4%) on endoscopy, three (6.3%)

on bariatric surgery, and two (4.2%) on endocrine surgery. Five (10.4%) consultants worked as full-time acute-care surgeons.

5.2.2 OUTCOMES BASED ON SURGEON'S EDUCATIONAL STATUS

Table 6 shows outcomes of consultants, residents, and residents assisted by consultants. Residents assisted by consultants had the highest conversion rates compared with consultants or residents only (25.6% *vs.* 21.6% *vs.* 8.5%, p<0.001). Similarly, residents assisted by consultants had the highest BDI rate (4.1% *vs.* 2.1% *vs.* 0.9%, p=0.041) and longest operating times (117 min *vs.* 90 min *vs.* 96 min, p<0.001) compared with consultants and residents only.

Figure 6 shows funnel plots of outcomes based on lead surgeon status. Seven (9.2%) of 76 surgeons had conversion rates above the 95% control limit and this remained unchanged by case-mix adjustment. Similarly in postoperative complications, four (5.3%) surgeons had rates above the upper 95% limit, and following case-mix adjustment, four surgeons remained above the upper 95% and one surgeon's complication rate fell below the lower 95% limit following adjustment.

TABLE 6. OUTCOMES IN STUDY II BASED ON SURGEONS' EDUCATIONAL STATUS.

	CONSULTANT (n=334) n (%)	RESIDENT (n=316) n (%)	RESIDENT ASSISTED BY CONSULTANT (n=242) n (%)	P
Conversion	72 (21.6)	27 (8.5)	62 (25.6)	**<0.001**
Adjusted conversion	21.7%	9.4%	22.8%	
Operating time, min (median, IQR)	90 (65-118)	96 (77-121)	117 (93-144)	**<0.001**
Postoperative complications	76 (22.8)	60 (19.0)	54 (22.3)	0.454
Adjusted complications	22.1%	20.9%	20.7%	
BDIs	7 (2.1)	3 (0.9)	10 (4.1)	**0.041**

BDI Bile duct injury IQR Interquartile range

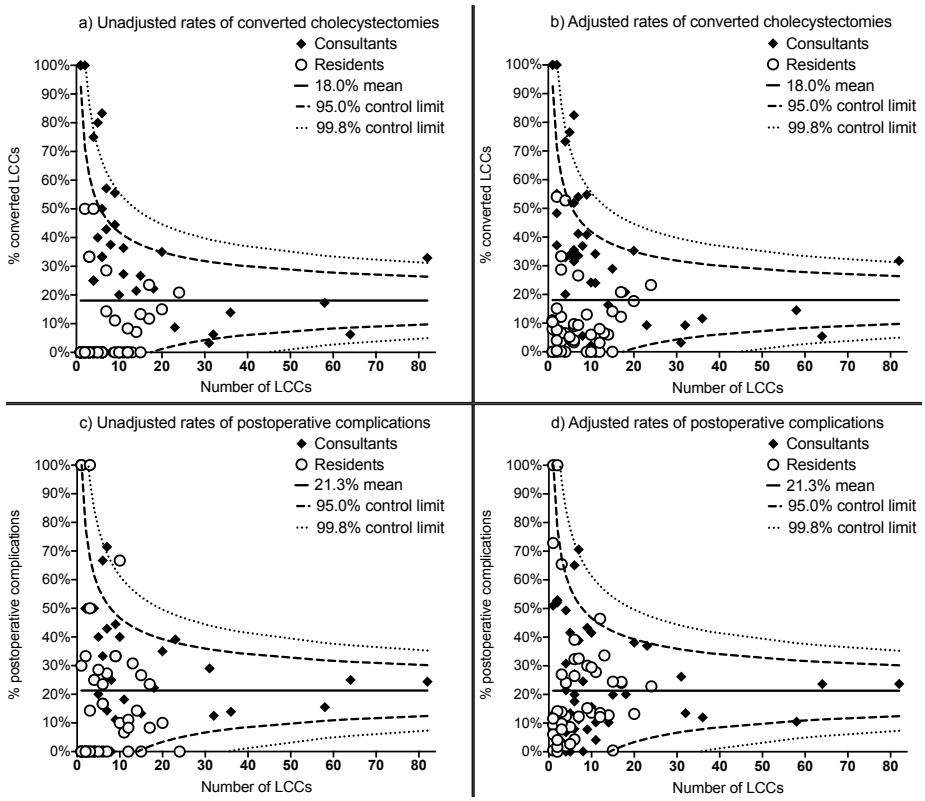

Figure 6 Funnel plots of outcome based on lead surgeon status. Consultants (n=28) performed 334 laparoscopic cholecystectomies (LCCs) and residents (n=48) performed 558. Thirteen surgeons graduating during residency are categorized into the category in which they had most procedures.

5.2.3 OUTCOMES BASED ON SURGEON'S ANNUAL VOLUME

The results of high-volume (> 5 LCCs for acute cholecystitis annually) *vs.* low-volume (≤ 5 emergency LCCs for acute cholecystitis) are presented in Table 7 and 8 in regard to all surgeons and consultants only, respectively. High-volume surgeons operated faster (91 *vs.* 108 min, <0.001) but did not differ from low-volume surgeons regarding conversions (19.6% *vs.* 16.6%, p=0.246) and postoperative complications (20.3% *vs.* 22.3%, p=0.467). High-volume consultants had lower conversion rates (15.6% vs. 33.2%, p=0.001) and operated faster (95 min *vs.* 110 min, p<0.001) compared with low-volume consultants.

TABLE 7. OUTCOMES FOR ALL SURGEONS IN STUDY II.

	HIGH-VOLUME (N=434) n, (%)	LOW-VOLUME (N=458) n, (%)	P
Conversion	85 (19.6)	76 (16.6)	0.246
Adjusted conversion	18.6%	17.4%	0.646
Operating time, min (median, IQR)	91 (69-120)	108 (85-132)	<**0.001**
Postoperative complications	88 (20.3)	102 (22.3)	0.467
Adjusted complications	19.1%	23.7%	0.094
BDIs	12 (2.8)	8 (1.7)	0.305

BDI Bile duct injury IQR Interquartile range

TABLE 8. OUTCOMES FOR SURGERIES WITH CONSULTANTS IN STUDY II.

	HIGH-VOLUME (n=326) n, (%)	LOW-VOLUME (n=250) n, (%)	P
Conversion	51 (15.6)	83 (33.2)	**<0.001**
Adjusted conversion	14.9%	31.8%	**<0.001**
Operating time, min (median, IQR)	95 (67-123)	110 (87-142)	**<0.001**
Postoperative complications	72 (22.1)	58 (23.2)	0.751
Adjusted complications	20.3%	23.2%	0.402
BDIs	8 (2.5)	9 (3.6)	0.421

BDI Bile duct injury IQR Interquartile range

5.3 STUDY III

5.3.1 PATIENT CHARACTERISTICS

Of the 1532 patients, 851 (55.5%) had gallstone disease with biliary colic, 549 (35.8%) had acute cholecystitis, 71 (4.6%) had symptomatic bile duct stones, 47 (3.1%) had biliary pancreatitis, and 14 (0.9%) had other diagnoses. A total of 851 (55.5%) patients had elective surgery, and 681 (45.5%) patients emergency surgery. The lead surgeon was a consultant GI surgeon in 769 (50.2%) of the surgeries.

Of the patients, 1177 (76.8%) had two photos of intraoperative CVS each. The median (IQR) CVS score was 3 (1.5-3.5), and 354 (23.1%) patients had a satisfactory CVS (score ≥ 4.5). The weighted kappa statistic for inter-rater agreement for the scores (0-6) was 0.36 for the anterior view, indicating fair agreement, 0.42 for the posterior view, indicating moderate agreement, and 0.33 for the doublet score, indicating fair agreement. The kappa statistic for the doublet score as categorical (satisfactory/unsatisfactory) was 0.37, indicating fair agreement.

5.3.2 PHOTO DOCUMENTED CVS AND BDIS

Table 9 compared patients with satisfactory CVS, unsatisfactory CVS, and missing photos. Patients with unsatisfactory CVS or missing photos were older, and had more comorbidities and emergency LCCs than patients with

satisfactory CVS. In emergency LCCs only, patients with unsatisfactory CVS had significantly higher CRP levels and higher WBCC than patients with satisfactory CVS. Of patients with acute cholecystitis, 86 (15.7%) of 549 patients had satisfactory CVS, whilst 263 (26.8%) of 983 without cholecystitis had satisfactory CVS, (p=<0.001).

TABLE 9. PATIENTS (N=1532) WITH SATISFACTORY, UNSATISFACTORY CVS OR MISSING PHOTOS.

	CVS SATISFACTORY (N=354) (%)	CVS UNSATISFACTORY (N=823) (%)	PHOTO MISSING (N=355) (%)	P
ALL LCCS				
Sex: male	105 (29.7)	323 (39.2)	144 (40.6)	**0.003**
Age, mean (IQR)	53 (39-67)	56 (42-69)	59 (46-72)	**<0.001**
Diabetes	20 (5.6)	84 (10.2)	39 (11.0)	**0.023**
ASA category > 2	99 (28.0)	274 (33.3)	162 (45.6)	**<0.001**
Length of surgery, min (median, IQR)	63 (51-88)	82 (63-109)	82 (60-113)	**<0.001**
EMERGENCY LCCS ONLY	116 (32.8)	398 (48.4)	167 (47.0)	**<0.001**
CRP, median (IQR)[1]	109 (31-168)	143 (53-239)	126 (46-225)	**0.004**
WBCC, median (IQR)[1]	12.0 (8.8-15.0)	13.1 (9.9-16.9)	12.3 (9.8-16.7)	**0.009**
Surgical findings:				
Acute cholecystitis	85 (73.3)	325 (81.7)	138 (82.6)	**0.097**
Gangrene	14 (12.1)	109 (27.4)	48 (28.7)	**0.002**

[1]CRP and WBCC missing in 11 patients

ASA American Society of Anesthesiologists CRP C-reactive protein CVS Critical view of safety IQR Interquartile range LCC Laparoscopic cholecystectomy WBCC White blood cell count

BDIs are presented in Table 10. The overall BDI rate was 1.1% with 0.3% for severe BDIs (Strasberg D-E). Emergency and elective LCCs had 9 (1.3%) BDIs of which 2 (0.3%) were severe, and 8 (0.8%) BDIs of which 2 (0.2%) were severe, respectively. Patients with satisfactory CVS had the lowest BDI rate compared with patients with unsatisfactory CVS or without photos (0.3% *vs.* 1.0% *vs.* 2.3%, p=0.012). Satisfactory CVS patients experienced only Strasberg type A injuries Three BDIs were Strasberg type E, where the CBD was completely transected. Two of these patients had no photos of attempted CVS, and the third patient had an unsatisfactory CVS score of 1.0. All three injuries were noted intraoperatively and treated with primary hepaticojejunostomy.

TABLE 10. BILE DUCT INJURIES IN STUDY III.

STRAS-BERG	CVS SATISFACTORY (n=354) (%)	CVS UNSATISFACTORY (n=823) (%)	PHOTO MISSING (n=355) (%)	TOTAL (n=1532)	P
A	1 (0.3)	6 (0.7)	6 (1.7)	13 (0.8)	
B					
C					
D		1 (0.1)		1 (0.1)	
E		1 (0.1)	2 (0.6)	3 (0.2)	
Total	1 (0.3)	8 (1.0)	8 (2.3)	17 (1.1)	**0.012**

CVS Critical view of safety

5.3.3 PHOTO DOCUMENTED CVS AND POSTOPERATIVE COMPLICATIONS

Table 11 presents rates of postoperative complications. The most severe complication was reported for each patient. Patients with satisfactory CVS had the lowest postoperative complication rate compared with patients with unsatisfactory CVS or without photos (4.8% *vs.* 7.9 *vs.* 9.9%, p=0.011). Furthermore, patients with satisfactory CVS had no Clavien-Dindo class 4 or 5 complications.

TABLE 11. POSTOPERATIVE COMPLICATIONS IN STUDY III.

CLAVIEN -DINDO CLASS	CVS SATISFACTORY (N=354) (%)	CVS UNSATISFACTORY (N=823) (%)	PHOTO MISSING (N=355) (%)	TOTAL (N=1532) (%)	P
1	2 (0.6)	5 (0.6)	3 (0.8)	10 (0.7)	
2	8 (2.3)	30 (3.6)	13 (3.7)	51 (3.3)	
3A	6 (1.7)	20 (2.4)	10 (2.8)	36 (2.3)	
3B	1 (0.3)	2 (0.3)	5 (1.4)	8 (0.5)	
4		4 (0.1)	2 (0.6)	6 (0.4)	
5		4 (0.1)	2 (0.6)	6 (0.4)	
Total	17 (4.8)	65 (7.9)	35 (9.9)	117 (7.6)	**0.011**

CVS Critical view of safety

5.4 STUDY IV

5.4.1 PATIENT AND SURGEON CHARACTERISTICS

In Study IV, the 1532 patients from Study III were analysed with the addition of 89 emergency LCC patients (with conversion before dissection of Calot's triangle) for a subgroup analysis. The diagnoses of the patients in Study IV are mentioned under Study III as well as the inter-rater agreement for the raters.

In total, 56 consultants and 51 residents performed 1532 LCCs. The lead surgeon was a consultant GI surgeon in 769 (50.2%) of the surgeries. Consultants performed 496 (58.3%) of the elective and 273 (40.1%) of the emergency surgeries. The residents' mean age in 2018 was 35 (range 30-51), and 30 (58.8%) were women. The consultants' mean age was 48 (range 33-67), and 32 (57.1%) were women.

5.4.2 CVS UTILISATION AMONG RESIDENTS AND CONSULTANTS

Forty-six surgeons answered the questionnaire before the intervention lecture. Of them, 33 were consultants and 13 were residents. Four (8.3%) reported over 50 LCCs in the last year, and 16 (33.3%) reported under 10 LCCs in the last year. Of the consultants, 27 (81.8%) reported knowing CVS, as did 10 (76.9%) of the residents. Three (9.1%) consultants listed all three criteria correctly, as did 2 (15.4%) residents. When asked about actions if CVS could not be achieved, 27 (56.3%) listed the fundus first method, 24 (50.0%) listed conversion and 7 (14.6%) listed cholangiography.

Patient characteristics and outcomes of 851 elective LCCs are presented in Table 12. Residents more often took photos (82.0% vs. 75.0%, p=0.016) and achieved higher rates of satisfactory CVS compared with consultants in all procedures (34.9% *vs.* 23.0%, p<0.001). When looking at photographed LCCs only, residents still had higher rates of satisfactory CVS (42.6% *vs.* 30.6%, p=0.001). The rate of satisfactory CVS remained higher for residents after case-mix adjustment as well. Consultants operated faster compared with residents (63 min *vs.* 70 min, p<0.001). No differences in BDI rates or postoperative complication rates emerged.

Patient characteristics and outcomes of 681 emergency LCCs are presented in Table 13. Consultants operated faster than residents (83 min *vs.* 104 min, p<0.001). No significant differences in satisfactory CVS, BDI or postoperative complication rates emerged both before and after case-mix adjustment.

TABLE 12. OUTCOME IN 851 ELECTIVE LCCS IN STUDY IV BASED ON EDUCATIONAL STATUS.

	RESIDENTS (N=355) (%)	CONSULTANT (N=496) (%)	P
OUTCOMES			
Photo taken	291 (82.0)	372 (75.0)	**0.016**
Median CVS score	4 (2-5)	3 (1.5-4.5)	**0.001**
Length of surgery, median (IQR)	70 (58-87)	63 (48-79)	**<0.001**
BDI	2 (0.6)	6 (1.2)	0.480
Postoperative complications	21 (5.9)	22 (4.4)	0.331
Overall satisfactory CVS	124 (34.9)	114 (23.0)	**<0.001**
Satisfactory CVS in LCCs with photo	124 (42.6)	114 (30.6)	**0.001**
CASE-MIX ADJUSTED OUTCOMES			
Overall satisfactory CVS	34.8%	23.0%	**<0.001**
Satisfactory CVS in LCCs with photo	42.4%	30.8%	**0.002**

BDI Bile duct injury CVS Critical view of safety IQR Interquartile range LCC Laparoscopic cholecystectomy

TABLE 13. OUTCOMES IN 681 EMERGENCY LCCS IN STUDY IV BASED ON EDUCATIONAL STATUS.

	RESIDENTS (N=408) (%)	CONSULTANTS (N=273) (%)	P
OUTCOMES			
Photo taken	308 (75.5)	206 (75.5)	0.992
Median CVS score	3 (1.5-4)	3 (1.5-4)	0.367
Length of surgery, median (IQR)	104 (82-128)	83 (62-115)	**<0.001**
BDI	5 (1.2)	4 (1.5)	1.000
Postoperative complications	45 (11.0)	29 (10.6)	0.867
Overall satisfactory CVS	75 (18.4)	41 (15.0)	0.252
Satisfactory CVS in LCCs with photo	75 (24.4)	41 (19.9)	0.237
CASE-MIX ADJUSTED OUTCOMES			
Overall satisfactory CVS	18.1%	15.4%	0.358
Satisfactory CVS in LCCs with photo	23.9%	20.5%	0.368

BDI Bile duct injury CVS Critical view of safety IQR Interquartile range LCC Laparoscopic cholecystectomy

5.4.3 EFFECT OF TEACHING INTERVENTION ON PHOTO DOCUMENTATION OF CVS

Halfway through the study, in March 2019, an intervention lecture on safe LCC and CVS was given. The rate of emergency LCCs was higher before the intervention (51.4% *vs.* 39.2%, p<0.001). The rate of photographed LCCs increased from 74% to 79%, (p=0.022) following the intervention, but no significant differences in satisfactory CVS, BDIs and operating time before and after the lecture emerged.

5.4.4 SATISFACTORY CVS AND QUARTILES OF PERFORMANCE

The results of surgeons categorized into 25% (lower), 25-75% (middle) and >75% (upper) quartiles of performance in satisfactory CVS are shown in Table 14 for elective LCCs and emergency LCCs in Table 15. In elective LCCs, surgeons in the upper quartile operated the fastest (62 min) compared with surgeons in the middle (66 min) and lower quartiles (78 min) (p<0.001), but there were no significant differences in BDIs, postoperative complications or operating time. No significant differences among the groups in BDIs, postoperative complications or operating time arose.

Use of bail-out strategies based on quartile of performance in emergency LCCs is shown in Table 16. In total, 89 patients with conversion prior to dissection of the cystic duct and artery were added. Conversion rates were 16.7%, 7.6% *vs.* 16.1% (p<0.001) for lower, middle, and upper quartiles surgeons, respectively. To account for bias resulting from upper quartile surgeons converting more and thus achieving higher rates of satisfactory CVS, a sensitivity analysis (Tables 17 and 18), where quartiles of performance were calculated of all 770 procedures (including the 89 patients with conversion prior to dissection of the cystic duct and artery) with unsatisfactory CVS, missing photos and conversion grouped into the same category. Table 17 shows outcomes in emergency LCCs, and Table 18 shows the use of bail-out strategies. Surgeons in the lower quartile for satisfactory CVS had the highest conversion rate compared with middle and upper quartile surgeons (18.1% *vs.* 9.8% *vs.* 12.5%, p=0.026). Upper quartile surgeons used the fundus first method more often compared with middle and lower quartile surgeons (3.9% *vs.* 1.2% *vs.* 1.1%, p=0.042).

TABLE 14. OUTCOMES IN 851 ELECTIVE LCCS WITH 62 SURGEONS ACCORDING TO QUARTILES OF MEAN SATISFACTORY CVS RATES.

	LOWER QUARTILE 16 SURGEONS (N=73) (%)	MID-QUARTILES 31 SURGEONS (N=564) (%)	UPPER QUARTILE 15 SURGEONS (N=214) (%)	P
Mean LCCs/surgeon (SD)	5 (6)	18 (11)	14 (14)	**<0.001**
Overall satisfactory CVS	0 (0.0)	127 (22.5)	111 (51.9)	**<0.001**
BDI	1 (1.4)	5 (0.9)	2 (0.9)	0.922
Postoperative complications	5 (6.8)	30 (5.3)	8 (3.7)	0.510
Case-mix adjusted postoperative complications	5.8%	5.6%	3.6%	
Operating time, min, median (IQR)	78 (67-97)	66 (52-83)	62 (51-82)	**<0.001**

BDI Bile duct injury CVS Critical view of safety IQR Interquartile range LCC Laparoscopic cholecystectomy SD Standard deviation

TABLE 15. OUTCOMES IN 681 EMERGENCY LCCS WITH 96 SURGEONS ACCORDING TO QUARTILES OF MEAN SATISFACTORY CVS RATES.

	LOWER QUARTILE 51 SURGEONS (N=145) (%)	MID-QUARTILES 22 SURGEONS (N=307) (%)	UPPER QUARTILE 23 SURGEONS (N=229) (%)	P
Mean emergency LCCs/surgeon (SD)	3 (4)	14 (6)	10 (9)	**<0.001**
Overall satisfactory CVS	0 (0.0)	37 (12.1)	79 (34.5)	**<0.001**
BDI	2 (1.4)	3 (1.0)	4 (1.7)	0.741
Postoperative complications	14 (9.7)	38 (12.4)	22 (9.6)	0.517
Adjusted postoperative complications	9.7%	12.4%	9.7%	
Operating time, min, median (IQR)	101 (71-129)	96 (74-125)	98 (71-121)	0.724

BDI Bile duct injury CVS Critical view of safety IQR Interquartile range LCC Laparoscopic cholecystectomy SD Standard deviation

TABLE 16. BAIL-OUT STRATEGIES IN 770 EMERGENCY LAPAROSCOPIC CHOLECYSTECTOMIES (INCLUDING CONVERSIONS) WITH 96 SURGEONS CATEGORISED INTO QUARTILES BASED ON THEIR MEAN SATISFACTORY CRITICAL VIEW OF SAFETY RATES.

	LOWER QUARTILE 51 SURGEONS (N=174) (%)	MID-QUARTILES 22 SURGEONS (N=329) (%)	UPPER QUARTILE 23 SURGEONS (N=267) (%)	P
Conversion	29 (16.7)	25 (7.6)	43 (16.1)	**<0.001**
Case-mix adjusted conversion	14.9%	8.1%	16.4%	
Fundus first	2 (1.1)	4 (1.2)	10 (3.7)	0.061

TABLE 17. OUTCOMES IN 770 EMERGENCY LCCs (INCLUDING CONVERSION) WITH 96 SURGEONS CATEGORISED INTO QUARTILES BASED ON THEIR MEAN SATISFACTORY CVS RATES.

	LOWER QUARTILE 51 SURGEONS (N=177) (%)	MID-QUARTILES 25 SURGEONS (N=338) (%)	UPPER QUARTILE 20 SURGEONS (N=255) (%)	P
Mean emergency LCCs/surgeon (SD)	4 (3)	14 (7)	13 (10)	**<0.001**
Overall satisfactory CVS	0 (0.0)	37 (10.9)	79 (31.0)	**<0.001**
BDI	4 (2.3)	4 (1.2)	5 (2.0)	0.612
Postoperative complications	27 (15.3)	44 (13.0)	29 (11.4)	0.498
Adjusted postoperative complications	14.6%	13.2%	11.6%	
Operating time, min, median (IQR)	113 (75-143)	98 (75-128)	100 (72-129)	0.097

BDI Bile duct injury CVS Critical view of safety IQR Interquartile range LCC Laparoscopic cholecystectomy SD Standard deviation

TABLE 18. BAIL-OUT STRATEGIES IN 770 EMERGENCY LAPAROSCOPIC CHOLECYSECTOMIES (INCLUDING CONVERSIONS) WITH 96 SURGEONS CATEGORISED INTO QUARTILES BASED ON THEIR MEAN SATISFACTORY CRITICAL VIEW OF SAFETY RATES.

	LOWER QUARTILE 51 SURGEONS (N=177) (%)	MID-QUARTILES 25 SURGEONS (N=338) (%)	UPPER QUARTILE 20 SURGEONS (N=255) (%)	P
Conversion	32 (18.1)	33 (9.8)	32 (12.5)	**0.026**
Case-mix adjusted conversion	15.7%	10.4%	12.6%	
Fundus first	2 (1.1)	4 (1.2)	10 (3.9)	**0.042**

6 DISCUSSION

6.1 RISK IDENTIFICATION FOR CONVERSION AND POSTOPERATIVE COMPLICATIONS IN ACUTE CHOLECYSTITIS

Study I identified diabetes, CRP > 150, age over 65 years, gangrene, and abscess as independent risk factors for conversion. Male sex, impaired renal function, age over 65 years, and conversion emerged as independent risk factors for postoperative complications. The conversion rates of 23.0% (Study I) and 18.0% (Study II) for acute cholecystitis were high compared with 6-18% conversion rates reported in literature (7,8,10-12).

In line with previous studies, severe inflammation characterized by high CRP, gangrene and abscess formation in acute cholecystitis, is a strong predictor for conversion and a difficult procedure (161,227,228). Furthermore, old patients with diabetes are at higher risk of developing severe inflammation due to susceptibility of infections and masking of symptoms onset (114,229).

As for postoperative complications, high age and impaired renal function independently raise the risk of all surgical complications. Converted patients might be at higher risk due to the increased risk of surgical site infections. Furthermore, as severe inflammation raises the risk of conversion, it raises the risk of postoperative complications as well. Converted surgeries are often longer, and prolonged operating time increases the risk of embolies, strokes and pneumonia (230). Male sex has been linked to complications in other studies as well (231), and speculated to be related to differences in physiology and delays in seeking medical care (229).

Knowledge of risk factors is important when planning the procedure and choosing, which surgeon to allocate the procedure to. But how can these risk factors be identified and influenced? Risk factors such as male sex, diabetes and impaired renal function may not be affected once the patient has been admitted, but delay to operation and patient allocation and selection may.

To avoid progression to severe inflammation, guidelines recommend that patients admitted for acute cholecystitis should be operated on as soon as possible (86,100). Studies have reported that patients should be operated on at least within 72 hours from admission to lower postoperative complications and length of stay (113). Furthermore, previous episodes of biliary colic, biliary pancreatitis and obstructive jaundice have been identified as risk factors for both conversion and complications in elective LCCs as well (70,232). Hence, it could be argued that patients presenting with their first episode of symptomatic gallstones, should be admitted for LCC during the same hospital-stay. However, in practice, problems in operating room resourcing is usually the reason behind delays in LCC.

Apart from using clinical judgement when planning LCCs, guiding risk scores to identify patients with elevated risk of adverse outcomes have been developed. Patients at high risk might benefit from being operated on by experienced surgeons, whilst some patients should be considered for alternative approaches such as PTC. Nevertheless, none of the proposed risk scores have been validated.

Onoe *et al.* proposed a risk score based on CRP, gallstone impactation and symptoms duration that predicted operating difficulty in terms of achieving CVS and recommended patients with high scores only be operated on by experienced surgeons (227).

Burke *et al.* proposed a risk score for predicting Clavien-Dindo IV and V complications based on patient age, preoperative sepsis, estimated glomerular filtration rate, preoperative albumin and planned open procedure (172). Patients with high scores might be considered for alternative approaches such as antimicrobial therapy and percutaneous drainage. Burke *et al.* recognized preoperative hypoalbuminemia as a risk factor for a difficult procedure. However, studies on patients who have received albumin infusion preoperatively have not had better outcomes, indicating low albumin as a substitute variable for severe kidney or liver disease instead of an independent risk factor for complications (172,233,234).

The Tokyo Guidelines recommend the use of percutaneous drainage over LCC for patients who are critically ill or considered surgically high-risk patients (100). Controversy on the management on high-risk patients still exists, and the Tokyo guidelines have been criticized for not recommending early LCC to patients with grade II or III acute cholecystitis (105). In the randomized controlled CHOCOLATE trial, however, high risk surgical patients who received LCC compared with percutaneous draining had fewer complications, fewer reinterventions and shorter hospital-stays (120). However, the study excluded patients with an APACHE II (121) score over 15 and patients receiving intensive care at diagnosis since the risk of mortality was deemed too high. Furthermore, none of the patients who received LCC had an ASA class of IV, and only 4.0% of patients assigned to the percutaneous drainage group and an ASA class of IV. In comparison, of patients with acute cholecystitis in Study I and II, 138 (15.5%) had an ASA class of IV and three (0.3%) patients had class V. This burden of comorbidities could partially explain the high conversion rates of 23% and 18.0% reported in Study I and II, respectively.

6.2 SURGEONS' EXPERIENCE AND OUTCOMES IN ACUTE CHOLECYSTITIS

LCC under inflamed and scarred conditions in acute cholecystitis is remarkably harder than for elective LCC. Surgeons have hence questioned whether residents should be allowed to perform LCC for acute cholecystitis. The Tokyo Guidelines recommend that Grade I-II cholecystitis may be operated on by residents, but Grade III should be operated on by experienced surgeons only (26). Study II supports that with the right patient selection, residents may operate on acute cholecystitis, as there were no more adverse outcomes in LCCs with residents as lead surgeons compared with consultants. Lien *et al.* similarly noted that consultants had shorter operating times than residents, yet no difference in conversion rates was observed (191). However, in Study II, the conversion and BDI rate was the highest in procedures with residents as lead surgeons assisted by consultants. Based on the operative note, however, it could not be deduced whether the consultant had been present from the beginning or summoned to help. These procedures might have been unpredictably difficult, leading to higher conversion rates. Scoring systems, as mentioned previously, might be helpful here as well, when choosing whom to allocate the procedures to.

In Study II, high-volume consultants had lower conversion rates than low volume-consultants. Consultants with high conversion rates might have gained inefficient training to begin with or lacked continuous training to maintain skills. Furthermore, they could have been focusing more on open than laparoscopic surgery during daily working hours and felt more comfortable with open cholecystectomy. Brown *et al.* found that on average 90 LCCs are required for the surgeon to master the procedure independently (235). With annual caseloads as low as in Study II, surgeons might not reach the needed caseloads for mastering LCC for acute cholecystitis. Once working as a consultant, developing this skill further might be challenging, since whilst working on-call, there usually is no one more experienced to relieve them in a demanding LCC. Moreover, surgeons in the early stages of their career might feel more comfortable with a laparoscopic procedure compared with surgeons in the last years of their career, since LCC became the standard technique as late as in the 1990s. Several studies have noted lower conversion and postoperative complication rates with rising annual and cumulative caseload (216,236,237). In Study II, no difference in postoperative complication rates regarding surgeon experience emerged, but this may strongly be influenced by patient selection.

Interestingly, however, the surgeon with the highest annual volume (Fig 5), had the highest conversion rates in Study II. This might be well an example of stagnated skill set as described by Ericsson *et al.* (207). Funnel plots might be handy in raising awareness for surgeons performing below the average, who might benefit from learning from those performing above the average.

Guarantying satisfactory numbers of LCCs per surgeon at a university hospital with many surgeons might be tricky. In Study II, surgeons performed on average 2.9 LCCs for acute cholecystitis a year - a remarkably low number. Nevertheless, data on the annual number of elective LCCs was missing in Study II. In Study IV, however, more surgeons were involved in performing emergency LCCs than elective LCCs, resulting in fewer procedures per surgeon and less experience in challenging conditions of acute cholecystitis. Residents might, therefore, not gain sufficient practical experience in acute cholecystitis. Furthermore, in Study IV, in emergency LCCs, surgeons in the lowest performance quartile for satisfactory CVS also had the lowest caseload (4 LCCs / surgeon/1.5 years) and the highest conversion rate, suggesting that surgeons with low annual caseloads might experience challenges in emergency LCC leading to both unsatisfactory CVS and high conversion rates. Surgeons in the upper quartile of satisfactory CVS use used the fundus first technique most, suggesting higher skill in using bail-out techniques. The high conversion rates of 23% in Study I and 18.0% in Study II could further be due to the high number of surgeons performing LCC at the institution, leading to insufficient numbers of LCC per surgeon.

Annual caseloads are influenced by several factors, including operating time allocated to emergency surgeries in daytime. Allocating all LCCs to only a few senior consultants would not be feasible, since all surgeons doing on-calls should exhibit sufficient skills in performing LCC for acute cholecystitis. As with the Tokyo guidelines, patients with moderate to severe cholecystitis, should preferably be treated by a laparoscopically advanced surgeon. However, even centralizing the treatment of these patients in daytime to laparoscopically advanced surgeons is impossible, and the surgeons on-call might not be laparoscopically advanced. However, if the patient stabilizes and responds well to antibiotics and general care, then the operation might be postponed until the next day. In a retrospective study, Andrews *et al.* found that by centralizing their around 450 annual elective LCCs from eight to four surgeons, the conversion rate decreased from 4.9% to 3.5% (p=0.016) (215).

In addition, residents' skill and experience in OC has raised concern. Even though a resident is sufficiently skilled in LCC, it would not convey into skill in OC. Initially, with the introduction of LCC, a spike in BDIs was seen. In a case series on 12 patients with major BDIs (Strasberg E), 10 of 12 BDIs occurred within each surgeon's first 11 LCCs, whilst the other two were the surgeons' 91st and 100th LCC (238). Such major injuries occurring immediately at the beginning of learning a new procedure conveys that these surgeons might have been over-confident in their own abilities and lacking sufficient senior support.

Due to the lack of structured surgical education, guarantying sufficient numbers of LCC per resident might be hard. Furthermore, evaluating and comparing programs is hard, since the structure of surgical

training programs vary significantly in terms of teaching methods and weekly hours, (205). Currently, residents are encouraged to keep a log of all procedures they perform, but there are no official guidelines on how many procedures a resident should perform during surgical training before graduating as a consultant in Finland. Furthermore, many surgical procedures like pancreas surgery and rectal surgery have been centralized to university hospitals to guarantee sufficient numbers per surgeon, but no audits on common procedures such as appendectomies or emergency LCCs within university hospitals have been done.

6.3 CVS AND PREVENTION OF MAJOR BDIS

The main purpose of CVS is to prevent major bile duct injury arising from anatomical misidentification. Minor BDIs related to cystic duct leaks from slipping clips or rotten tissues might not be prevented with the use of CVS. When implemented correctly, however, CVS could lower the risk of major choledochal injury.

In Study III, in LCCs with satisfactory CVS, no major BDIs occurred. This is well supported by other studies that have not reported any BDIs occurring with satisfactory photo or video documented CVS (15,21-23). More BDIs occurred in patients with unsatisfactory CVS and those without photo documentation. However, as seen in Table 9, these patients had more comorbidities and were older – factors that in themselves raise the risk of BDI.

Photo documented CVS works for several reasons. Firstly, the idea of CVS lies in in avoiding "error traps" in which the infundibular technique could fail like when a short cystic duct adheres closely to the gallbladder (147,149). CVS might take longer than other identification techniques as it requires more dissection to the cystic plate before clipping the structures. Nevertheless, this part needs to be dissected at some point, and by clearing the whole hepatocystic triangle, the surgeon accounts for anatomical variations such as multiple cystic arteries, the right hepatic artery running through the hepatocystic triangle, a short cystic duct adhering to the common hepatic duct or an accessory right hepatic duct. Secondly, by photo documentation of CVS, the surgeon is prone to perform more meticulous dissection since his or her work will be viewed by others – a phenomenon known as "the Hawthorne effect" in psychology (239). Video documentation instead photo documentation could further strengthen this effect (15,240,241).

However, the lack of level A evidence prevents drawing conclusions on the causality between satisfactory CVS and BDIs. All evidence so far is from observational retrospective studies. Conducting prospective randomized trials would be challenging taken the rarity of BDIs. With an incidence of around 0.3%, ca 4500 patients per arm would be needed to demonstrate a significant difference. Furthermore, in hospitals where CVS is

already commonly used, operating with other techniques than CVS could be met with reluctancy.

The CVS method has also received critique as CVS cannot be reached in all scenarios. Severe adhesions and scarring of the hepatocystic triangle might make it impossible to reach CVS. Many BDIs resulting from misidentification of anatomy occur due to dissection started out in the wrong plane, causing the wrong two structures (like the CBD and the right hepatic artery) to appear as the cystic duct and artery. However, in these cases. all three criteria of CVS would not be fulfilled, which should alert the surgeon to the potential risk of BDI. In these scenarios, inability to reach CVS should alert the surgeon to consider bail-out strategies such as subtotal cholecystectomy, intraoperative cholangiography, or conversion. For avoiding dissection in the wrong plane and BDI, Iskandar et al. propose starting dissection through the posterior infundibular approach (242).

The BDI rate in all studies in this thesis was high (1.1-2.2%) compared with the overall rates 0.5-1.5% reported by other studies (12,13,15-17). However, Study I and II included only acute cholecystitis, in which the BDI rate is remarkably higher compared with elective LCC. Furthermore, reporting BDIs in other studies is not straightforward. The ICD code system lacks codes for BDI, and in studies on large populations, the BDI reporting has been based on diagnosis code searches instead of manual examination of patient files. Furthermore, not all studies report cystic duct leaks as BDIs (12,14,15). In Study I-IV, we reported even suspected cystic duct leaks (significant biliary drain output or findings on MRI) in which no clear leak was visible on ERC. We chose to report these as all these patients received a treatment intervention (ERC and sphincterotomy with or without stenting) after which the biliary leak ceased.

6.4 INCREASING USE OF CVS

CVS is not achievable in all situations, when severe inflammation, adhesions, Mirizzi syndrome, or unexpected bleeding is present. Nevertheless, the high variation in satisfactory CVS among individual surgeons, and the poor knowledge demonstrated in the survey in Study IV tell us that the use of CVS could be higher, and more BDIs caused by anatomical misidentification could be prevented. Misconceptions on what constitutes CVS were evident among surgeons in the questionnaire, as around 80% stated being familiar with CVS, whilst only 10% were able to list all three criteria correctly. Similarly, Gupta *et al.* reported low knowledge of CVS among 259 residents in a survey study from 2021. 88.3% reported knowing CVS, whilst 15.1% named the three criteria correctly (24).

Surgery is taught in a master-apprentice type of fashion, where residents observe consultants and try to mimic the techniques they use. However, this kind of a learning strategy is largely subject to subjectivity and

personal preference, and a resident might find it difficult to distinguish which techniques to absorb and which to dismiss. Therefore, adherence to structured evidence-based guidelines on the best operating techniques serves both the surgeon and the patient. Major guidelines have not recommended CVS as recently as until 2018 and CVS is expected to gain more widespread use in the years to come (26).

Consultants had significantly lower rates of satisfactory CVS than residents, which might be explained by the rather recent introduction of CVS into the surgical field in 1995. Consultants have become routinised in other techniques and might lack the motivation to change their technique if it has previously worked well. Since BDIs are so rare, consultants are unlikely to experience more than a couple of these during their career and hence there is nothing that motivates a switch in technique.

In Study IV, the teaching lecture did not lead to a significant increase in satisfactory CVS rates. However, in their study, Nijssen *et al.* found that their teaching intervention raised use of CVS, and had most effect on GI surgery consultants, as they were able to achieve higher rates of satisfactory CVS compared with residents or general surgeons (23). This might indicate that surgeons with great laparoscopic skill are most adept to learning new techniques. Making photographing LCCs mandatory could also help raise the rate of CVS use as surgeons are likely to perform better, should their work be photo documented. Some countries, like the Netherlands, have made photographing all LCCs mandatory (27). However, the national BDI rate has not yet decreased in response to this, but this has been accounted to incorrect use of CVS.

As discussed, CVS can hardly be achieved in all procedures. But what rate of CVS is achievable? Implementing CVS as the standard operating technique would not drive the rate of BDI to null. Nevertheless, a unified standard technique would help avoiding error traps such as adherence of the cystic duct to the CBD or accessory right hepatic ducts. Furthermore, it would also alert the surgeon in cases when CVS cannot be achieved. If CVS could be achieved in 90% of LCCs for acute cholecystitis, a conversion rate of 10% could be acceptable. As seen in the survey on bile duct injuries, surgeons reported most BDIs after 100 LCCs (192). Similarly, in Study III, all class E injuries occurred with a consultant present. Hence, these injuries have probably not been due to underdeveloped knowledge of anatomy, but rather due to over-confidence resulting in thinking that the structure one has identified as the cystic duct cannot be anything else.

Furthermore, the unstructured surgical education in Finland is at risk due to the master-apprentice type of fashion. Consultant surgeons are also responsible for the technique they teach residents, and for residents, recognizing good mentors throughout their training might be hard. Therefore, clear evidence-based guidelines and structured surgical education would likely favor the implementation of CVS and quality of LCC.

The Dutch Society of Surgery recommended CVS in 2005 (25). In a questionnaire sent out to all members of the Dutch Society of Surgery, 97.6% of responding surgeons reported using CVS, and 47.2% documented it with photo and 30.2% with video (25). If CVS is not obtained, 50.9% of surgeons convert, 39.1% continue laparoscopically, and 10.0% perform additional imaging studies. Of Dutch surgeons, 53.2% never perform intraoperative cholangiography (IOC), 41.3% perform it incidentally, and only 2.6% perform it routinely. A similar operating strategy recommendation (Fig 7) by the Finnish Society of Surgeons could lead to rising use of CVS.

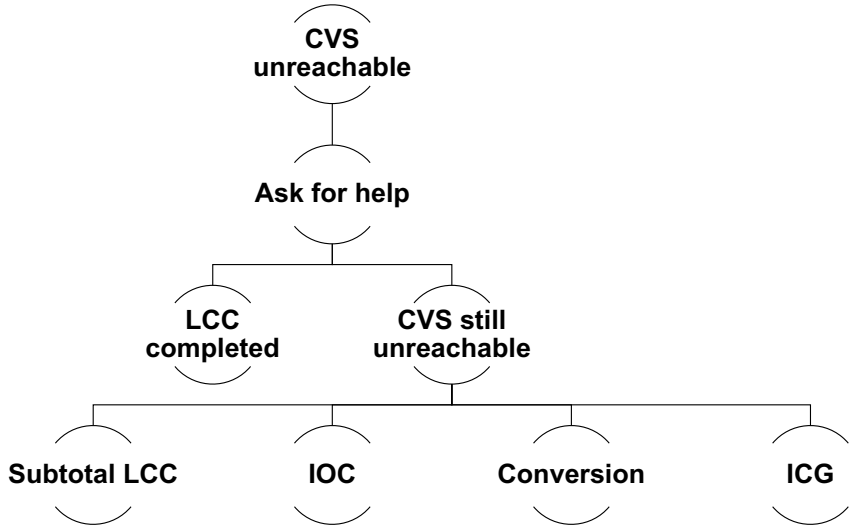

Figure 7. Bail-out strategies in case of unreachable Critical view of safety (CVS)
ICG Indocyanine green IOC Intraoperative cholangiography LCC Laparoscopic cholecystectomy

6.5 LIMITATIONS

The retrospective nature of data collection in all studies lead to several limitations as retrospective data collection is subject both to reporting and interpretation errors. Furthermore, in Study I data on symptoms duration and BMI was missing from many patients – both associated with conversion and complications in previous studies (115,220). Also, different risk factor's association with different postoperative complications in Study I could not be reliably evaluated due to the limited sample size. Furthermore, the risk factors were analysed using a stepwise forward regression model, which could have resulted in overfitting and falsely narrow confidence intervals.

Overall, in Study II, classifying surgeons based on their volume proved difficult as the annual number of LCCs per surgeon remained so low. Over 5 emergency LCCs a year cannot really be considered high-volume, but higher numbers could not really be chosen, since there were so few surgeons who performed higher numbers of LCC. Furthermore, classifying surgeries based on who acted as lead surgeon might have been biased as it was not always clear from the operating note how much the assistant participated – consultant surgeons might have performed substantial parts of the operation they assisted. Additionally, information on surgeons' previous cumulative caseloads was missing, as was the number of elective LCCs annually. The association of the surgeon's subspecialisation on the outcomes was also not accounted for.

The true rate of satisfactory CVS might have been subjected to several confounders. First, unphotographed LCCs might have been satisfactory for CVS. Second, the inter-rater agreement for CVS scores was only fair. Furthermore, the raters differed significantly in their criticalness in the ratings but using two raters for each picture instead of one might have balanced out some of the differences in criticalness. Also, choosing a mean score of ≥4.5 as satisfactory meant that no pictures with scores under 3 could be rated satisfactory, and at least one of the raters must have given a score of 5 or higher. Third, poor technical qualities of some pictures might have earned them lower ratings compared with what technically precise pictures would have received.

In Study III & IV, patients with unsatisfactory CVS or missing photos had more comorbidities and more severe inflammation. These factors in themselves raise the risk of BDI, and hence satisfactory CVS and no associated BDIs might be a result of easier procedures. The number of BDIs was in itself so low that its association with satisfactory CVS remained subject to chance and attempting a multivariate analysis on risk factors was not feasible as there were only 17 BDIs. Furthermore, as the study was retrospective in nature, no true causality between satisfactory CVS and BDIs could be established.

Case-mix adjustment with regression models was performed to account for selection bias when evaluating surgeons' conversion,

complication, and satisfactory CVS rates. Nevertheless, these models might have performed poorly, and hence, for example some residents might have achieved lower conversion rates and higher satisfactory CVS rates due to receiving easier LCCs.

6.6 FUTURE PROSPECTS

As discussed earlier, randomized-controlled trials on the treatment of high-risk surgical patients for acute cholecystitis have been scarcely conducted. The CHOCOLATE trial (120) aimed at comparing the use of LCC and percutaneous draining in high-risk surgical patients, but excluded the most high-risk patients. Furthermore, retrospective studies on patients with highest risks (APACHE score over 15, ASA class IV or more) are rare. Study I and II, however, contained several patients regarded ASA class IV or V who were treated with good outcomes and therefore prospective controlled trials on even the most high-risk patients could be considered in the future.

The lack of structured education in LCC in the surgical education is a severe problem. No official guidelines on recommended numbers of procedures before graduating exist. Prospective studies assessing surgeons' individual qualities and suitability for GI surgery are missing. Furthermore, implementing protocols for required standard of care such as satisfactory CVS benefits both the patient and the surgeon. In addition to individual lectures, implementing a time-out session in the operating room to establish CVS or ask for senior approval could help raise the use of CVS.

As discussed earlier, ability to reach CVS might act as a surrogate for an easier procedure, and RCTs are not feasible due to the low incidence of BDI. Hence, to further evaluate the effects of CVS on BDIs, surgeons, who actively strive for CVS in every LCC, could be compared with surgeons, who use other techniques, in terms of BDI rate.

7 CONCLUSIONS

I Advanced cholecystitis characterized by high CRP, gangrene or abscess increase the risk of conversion. Conversion is associated with a higher risk of postoperative complications.

II High-volume consultants have shorter operative times and lower conversion rates in LCC for acute cholecystitis than low-volume consultants.

III Intraoperative photo documentation of CVS is associated with an overall lower rate of BDIs. Implementing routine photo documentation of CVS in LCCs could potentially lower the rate of BDIs caused by misidentified anatomy.

IV Individual surgeons achieve CVS with considerable variation. Stronger interventions than single lectures might be needed to raise use of CVS.

ACKNOWLEDGMENTS

Finally, after some very long years of work, this thesis is finished. Even though its ability to change the world or win me a Nobel Prize may be limited, it certainly did change me. Starting out with the first project as a second-year medical student, I knew nothing. Having finished this, I am more sure than ever that I know nothing, but may now possess the tools to critically address this next to nothing knowledge.

The studies in this thesis were carried out at the Abdominal Center of Helsinki University Hospital and the University of Helsinki from 2015 to 2022. My heartfelt thanks go to everyone who has been involved in this thesis and supported me during this project.

I thank Professor *Pauli Puolakkainen* for the possibility of carrying out this study at the Department of Gastrointestinal Surgery.

I owe my deepest gratitude to my supervisors - adjunct professors *Panu Mentula* and *Ville Sallinen*. Thank you, *Panu*, for your endless encouragement and patience with my stubborn attempts at learning statistics, for always making time for me in your busy schedule and for treating me like an equal. *Ville*, I am forever grateful for your engagement, your ideas, and your enthusiasm. It has been a privilege to have the both of you as my thesis supervisors - support from two well-respected researchers and surgeons has meant the world to me.

I wish to express my gratitude to my co-authors *Ari Leppäniemi*, *Hanna Lampela, Jukka Harju* and *Laura Koskenvuo*. Thank you for taking the time to take part in my projects and for being thorough in your work. Thank you, professor *Joonas Kauppila* and adjunct professor *Jukka Karvonen*, for reviewing this thesis and for giving valuable and insightful comments.

People probably rarely realise when a small act of theirs hugely influences somebody's life. I am talking about *Carola Haapamäki,* whose workday I was able to follow as a second-year medical student. You gave me the chance to actively assist in a small bowel resection and recommended *Panu* as a thesis supervisor. Without your engagement, I might not have fallen in love with the atmosphere in the OR and would be on a completely different path.

All my colleagues at Kymenlaakso Central Hospital receive my warmest thanks for supporting me in both my research and clinical work. Thank you, *Pälvi Vento*, for both giving me an opportunity to work there and being part of the thesis committee. Thank you, *Inna Lupina, Päivi Palanne* and *Hanna*

Kokamägi for all the support, and lessons in life and surgery. A special thanks to *Mikko Teikari*, for your excellent sense of humour and for treating my Mom with the most critical of views. Thank you, *Aleksi, Niko* and *Ville* – my fellow residents in GI surgery – for teaching me everything you know, and for all the support and humour. Thank you, *Veera*, for being the best roommate and for lodging me through the first year of residency like a big sister. *Alar Tuvikene* deserves special thanks for routing for me from the start and for reminding me that there is more to life than work, even if these reminders often meant threatening to throw me out from the ER at the end of the day. I thank *Joonas* for his endless energy and for our therapeutical rants about life in the ER over coffee and chicken wings.

I thank my childhood friends *Paulina, Vivian, Henna, Ninni* and *Ida* for always being there for me through joys and sorrows. Thank you all my fellow course mates and friends from *Thorax -13* and *Cursus iMedicorum*. Endless heaps of gratitude are directed at *Kaisa* and *Jannica* – who have put up with my obsessive rants, calmed my nerves before presentations, and always managed to see the best in me when I was not able to. You are invaluable.

I thank my grandfather *Lasse* for teaching the value of hard work and an interest in academics to a little girl. I wish we would have had more time together. I thank my Mom*, Gina,* for all the sacrifices she made when raising me and my brothers, and for her indefinite support and love. I thank *Ali* for his support and interest in my studies and for his excellent expertise regarding cars. I thank my darling brothers *Philip, Danny* and *Martin* for filling my life with laughter and for never ceasing to challenge me. Being your big sister has developed my patience and argumentation skills - qualities that have proven valuable to an aspiring researcher and surgeon. Maybe a PhD will finally give me more authority in your eyes, yet somehow, I highly doubt it.

Helsinki, September 2022
Petra Terho

This work has been financially supported by Finska Läkaresällskapet, Victoriastiftelsen and the Abdominal Center of Helsinki University Hospital.

REFERENCES

1. Finnish Institute for Health and Wellfare. Periods of care with procedures by primary procedure 2014–2015, https://www.thl.fi/fi/tilastot/tilastot-aiheittain/erikoissairaanhoidon-palvelut/somaattinen-erikoissairaanhoito ; 2017. [Accessed on August 14th 2022]
2. Digital N.H.S.: Hospital Episode Statistics [HES], main procedures and interventions summary 2019–2020 , https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2019-20; 2020. [Acessed on August 14th 2022]
3. Keus F, Gooszen HG, van Laarhoven CJ. Open, small-incision, or laparoscopic cholecystectomy for patients with symptomatic cholecystolithiasis. An overview of Cochrane Hepato-Biliary Group reviews. Cochrane Database Syst Rev. 2010 Jan;2010(1):CD008318.
4. Coccolini F, Catena F, Pisano M, Gheza F, Fagiuoli S, Di Saverio S, et al. Open versus laparoscopic cholecystectomy in acute cholecystitis. Systematic review and meta-analysis. Int J Surg. 2015 Jun;18:196–204.
5. Kiviluoto T, Sirén J, Luukkonen P, Kivilaakso E. Randomised trial of laparoscopic versus open cholecystectomy for acute and gangrenous cholecystitis. Lancet. 1998;351(9099):321–5.
6. Krielen P, Stommel MWJ, Pargmae P, Bouvy ND, Bakkum EA, Ellis H, et al. Adhesion-related readmissions after open and laparoscopic surgery: a retrospective cohort study (SCAR update). Lancet. 2020 Jan;395(10217):33–41.
7. Giger UF, Michel J-M, Opitz I, Th Inderbitzin D, Kocher T, Krahenbuhl L. Risk factors for perioperative complications in patients undergoing laparoscopic cholecystectomy: analysis of 22,953 consecutive cases from the Swiss Association of Laparoscopic and Thoracoscopic Surgery database. J Am Coll Surg. 2006 Nov;203(5):723–8.
8. Jensen KK, Roth NO, Krarup P-M, Bardram L. Surgical management of acute cholecystitis in a nationwide Danish cohort. Langenbecks Arch Surg. 2019 Aug;404(5):589–97.
9. Livingston EH, Rege RV. A nationwide study of conversion from laparoscopic to open cholecystectomy. Am J Surg. 2004 Sep;188(3):205–11.
10. Coffin SJ, Wrenn SM, Callas PW, Abu-Jaish W. Three decades later: investigating the rate of and risks for conversion from laparoscopic to open cholecystectomy. Surg Endosc. 2018 Feb;32(2):923–9.
11. Sippey M, Grzybowski M, Manwaring ML, Kasten KR, Chapman WH, Pofahl WE, et al. Acute cholecystitis: risk factors for conversion to an open procedure. Journal of Surgical Research. 2015 Dec;199(2):357–61.

12. Kum CK, Eypasch E, Lefering R, Paul A, Neugebauer E, Troidl H. Laparoscopic cholecystectomy for acute cholecystitis: is it really safe? World J Surg. 1996 Jan;20(1):43–8–discussion48–9.
13. Pucher PH, Brunt LM, Davies N, Linsk A, Munshi A, Rodriguez HA, et al. Outcome trends and safety measures after 30 years of laparoscopic cholecystectomy: a systematic review and pooled data analysis. Surg Endosc. 2018 May;32(5):2175–83.
14. Barrett M, Asbun HJ, Chien H-L, Brunt LM, Telem DA. Bile duct injury and morbidity following cholecystectomy: a need for improvement. Surg Endosc. 2018 Apr;32(4):1683–8.
15. Nijssen MAJ, Schreinemakers JMJ, Meyer Z, van der Schelling GP, Crolla RMPH, Rijken AM. Complications After Laparoscopic Cholecystectomy: A Video Evaluation Study of Whether the Critical View of Safety was Reached. World J Surg. 2015 Jul;39(7):1798–803.
16. Fong ZV, Pitt HA, Strasberg SM, Loehrer AP, Sicklick JK, Talamini MA, et al. Diminished Survival in Patients with Bile Leak and Ductal Injury: Management Strategy and Outcomes. J Am Coll Surg. 2018 Apr;226(4):568–576.e1.
17. Kohn JF, Trenk A, Kuchta K, Lapin B, Denham W, Linn JG, et al. Characterization of common bile duct injury after laparoscopic cholecystectomy in a high-volume hospital system. Surg Endosc. 2018 Mar;32(3):1184–91.
18. Strasberg SM, Hertl M, Soper NJ. An analysis of the problem of biliary injury during laparoscopic cholecystectomy. J Am Coll Surg. 1995 Jan;180(1):101–25.
19. Yegiyants S, Collins JC. Operative strategy can reduce the incidence of major bile duct injury in laparoscopic cholecystectomy. Am Surg. 2008 Oct;74(10):985–7.
20. Avgerinos C, Kelgiorgi D, Touloumis Z, Baltatzi L, Dervenis C. One thousand laparoscopic cholecystectomies in a single surgical unit using the “critical view of safety” technique. J Gastrointest Surg. 2009 Mar;13(3):498–503.
21. Chen CB, Palazzo F, Doane SM, Winter JM, Lavu H, Chojnacki KA, et al. Increasing resident utilization and recognition of the critical view of safety during laparoscopic cholecystectomy: a pilot study from an academic medical center. Surg Endosc. 2017 Apr;31(4):1627–35.
22. Stefanidis D, Chintalapudi N, Anderson-Montoya B, Oommen B, Tobben D, Pimentel M. How often do surgeons obtain the critical view of safety during laparoscopic cholecystectomy? Surg Endosc. 2017 Jan;31(1):142–6.
23. Nijssen MAJ, Schreinemakers JMJ, van der Schelling GP, Crolla RMPH, Rijken AM. Improving Critical View of Safety in Laparoscopic Cholecystectomy by Teaching Interventions. J Surg Educ. 2016 May;73(3):442–7.
24. Gupta V, Lal P, Vindal A, Singh R, Kapoor VK. Knowledge of the Culture of Safety in Cholecystectomy (COSIC) Among Surgical Residents: Do We Train Them Well For Future Practice? World J Surg. 2021 Apr;45(4):971–80.

25. Buddingh KT, Hofker HS, Cate Hoedemaker ten HO, van Dam GM, Ploeg RJ, Nieuwenhuijs VB. Safety measures during cholecystectomy: results of a nationwide survey. World J Surg. 2011 Jun;35(6):1235–41–discussion1242–3.
26. Wakabayashi G, Iwashita Y, Hibi T, Takada T, Strasberg SM, Asbun HJ, et al. Tokyo Guidelines 2018: surgical management of acute cholecystitis: safe steps in laparoscopic cholecystectomy for acute cholecystitis (with videos). J Hepatobiliary Pancreat Sci. 2018 Jan;25(1):73–86.
27. Ansaloni L, Pisano M, Coccolini F, Peitzmann AB, Fingerhut A, Catena F, et al. 2016 WSES guidelines on acute calculous cholecystitis. World J Emerg Surg. 2016;11:25.
28. Albers CJ, Huizenga JR, Krom RA, Vonk RJ, Gips CH. Composition of human hepatic bile. Ann Clin Biochem. 1985 Mar;22 (Pt 2):129–32.
29. Housset C, Chrétien Y, Debray D, Chignard N. Functions of the Gallbladder. Compr Physiol. 2016 Jun;6(3):1549–77.
30. Hartmann H, Petit-Dutaillis D. Les suites éloigneés de la cholecystéctomie . J Chirurgie. 1931;(20):349–57.
31. Benson EA, Page RE. A practical reappraisal of the anatomy of the extrahepatic bile ducts and arteries. Br J Surg. 1976 Nov;63(11):853–60.
32. Vakili K, Pomfret EA. Biliary anatomy and embryology. Surg Clin North Am. 2008 Dec;88(6):1159–74–vii.
33. DOWDY GSJ, WALDRON GW, BROWN WG. Surgical anatomy of the pancreatobiliary ductal system. Observations. Arch Surg. 1962 Feb;84:229–46.
34. Uesaka K, Yasui K, Morimoto T, Torii A, Yamamura Y, Kodera Y, et al. Visualization of routes of lymphatic drainage of the gallbladder with a carbon particle suspension. J Am Coll Surg. 1996 Oct;183(4):345–50.
35. Calot J-F. De la cholécystectomie. 1891. [Paris].
36. Abdalla S, Pierre S, Ellis H. Calot's triangle. Clin Anat. 2013 May;26(4):493–501.
37. Rouviere H. Sur la configuration et la signification du sillon du processus caude. Bulletins et memoires de la societe Anatomique de Paris. 1924;93:355–8.
38. Singh K, Ohri A. Anatomic landmarks: their usefulness in safe laparoscopic cholecystectomy. Surg Endosc. 2006 Nov;20(11):1754–8.
39. Andall RG, Matusz P, Plessis du M, Ward R, Tubbs RS, Loukas M. The clinical anatomy of cystic artery variations: a review of over 9800 cases. Surg Radiol Anat. 2016 Jul;38(5):529–39.
40. Singh K, Singh R, Kaur M. Clinical reappraisal of vasculobiliary anatomy relevant to laparoscopic cholecystectomy. J Minim Access Surg. 2017 Oct;13(4):273–9.
41. Taourel P, Bret PM, Reinhold C, Barkun AN, Atri M. Anatomic variants of the biliary tree: diagnosis with MR cholangiopancreatography. Radiology. 1996 May;199(2):521–7.

42. Schnelldorfer T, Sarr MG, Adams DB. What is the duct of Luschka?--A systematic review. J Gastrointest Surg. 2012 Mar;16(3):656–62.
43. Garg S, Kumar H, Sahni D, Yadav TD, Aggarwal A, Gupta T. Rare anatomic variations of the right hepatic biliary system. Surg Radiol Anat. 2019 Sep;41(9):1087–92.
44. WILLIAMS C, WILLIAMS AM. Abnormalities of the bile ducts. Ann Surg. 1955 May;141(5):598–606.
45. Scott-Conner CE, Hall TJ. Variant arterial anatomy in laparoscopic cholecystectomy. Am J Surg. 1992 Jun;163(6):590–2.
46. Boyden EA. The accessory gall-bladder– an embryological and comparative study of aberrant biliary vesicles occurring in man and the domestic mammals. American Journal of Anatomy. 1926;38(2):177–231.
47. Farhat W, Mabrouk MB, Ammar H, Mizouni A, Said MA, Lagha S, et al. Gallbladder volvulus: A case report and review of the literature. Int J Surg Case Rep. 2019;60:75–8.
48. Guiteau JJ, Fisher M, Cotton RT, Goss JA. Intrahepatic gallbladder. J Am Coll Surg. 2009 Nov;209(5):672.
49. Ehman RL, Morrish HF. Retrorenal gallbladder. A case report. J Can Assoc Radiol. 1983 Dec;34(4):321–2.
50. Muhrbeck O, Ahlberg J. Prevalence of gallstone disease in a Swedish population. Scand J Gastroenterol. 1995 Nov;30(11):1125–8.
51. Everhart JE, Khare M, Hill M, Maurer KR. Prevalence and ethnic differences in gallbladder disease in the United States. Gastroenterology. 1999 Sep;117(3):632–9.
52. Aerts R, Penninckx F. The burden of gallstone disease in Europe. Aliment Pharmacol Ther. 2003 Nov;18 Suppl 3:49–53.
53. Glambek I, Kvaale G, Arnesjö B, Søreide O. Prevalence of gallstones in a Norwegian population. Scand J Gastroenterol. 1987 Nov;22(9):1089–94.
54. Völzke H, Baumeister SE, Alte D, Hoffmann W, Schwahn C, Simon P, et al. Independent risk factors for gallstone formation in a region with high cholelithiasis prevalence. Digestion. 2005;71(2):97–105.
55. Shabanzadeh DM, Sørensen LT, Jørgensen T. Determinants for gallstone formation - a new data cohort study and a systematic review with meta-analysis. Scand J Gastroenterol. 2016 Oct;51(10):1239–48.
56. Attili AF, De Santis A, Capri R, Repice AM, Maselli S. The natural history of gallstones: the GREPCO experience. The GREPCO Group. Hepatology. 1995 Mar;21(3):655–60.
57. Shabanzadeh DM, Sørensen LT, Jørgensen T. A Prediction Rule for Risk Stratification of Incidentally Discovered Gallstones: Results From a Large Cohort Study. Gastroenterology. 2016 Jan;150(1):156–167.e1.
58. Qiao T, Ma R-H, Luo X-B, Yang L-Q, Luo Z-L, Zheng P-M. The systematic classification of gallbladder stones. PLoS One. 2013;8(10):e74887.

59. Wang DQ, Carey MC. Complete mapping of crystallization pathways during cholesterol precipitation from model bile: influence of physical-chemical variables of pathophysiologic relevance and identification of a stable liquid crystalline state in cold, dilute and hydrophilic bile salt-containing systems. J Lipid Res. 1996 Mar;37(3):606–30.
60. Cotton PB, Elta GH, Carter CR, Pasricha PJ, Corazziari ES. Rome IV. Gallbladder and Sphincter of Oddi Disorders. Gastroenterology. 2016 Feb.
61. Shabanzadeh DM, Sørensen LT, Jørgensen T. Which Abdominal Symptoms are Associated with Clinical Events in a Population Unaware of Their Gallstones? a Cohort Study. J Gastrointest Surg. 2017 May;21(5):831–9.
62. Abdelhamid MO, Thiels CA, Bingener J. Is functional gallbladder disease truly increasing? Results from the Rochester Epidemiology Project. Am J Surg. 2018 Nov;216(5):932–4.
63. Ahmed M, Diggory R. The correlation between ultrasonography and histology in the search for gallstones. Ann R Coll Surg Engl. 2011 Jan;93(1):81–3.
64. Shea JA, Berlin JA, Escarce JJ, Clarke JR, Kinosian BP, Cabana MD, et al. Revised estimates of diagnostic test sensitivity and specificity in suspected biliary tract disease. Arch Intern Med. 1994 Nov;154(22):2573–81.
65. McIntosh DM, Penney HF. Gray-scale ultrasonography as a screening procedure in the detection of gallbladder disease. Radiology. 1980 Sep;136(3):725–7.
66. Benarroch-Gampel J, Boyd CA, Sheffield KM, Townsend CMJ, Riall TS. Overuse of CT in patients with complicated gallstone disease. J Am Coll Surg. 2011 Oct;213(4):524–30.
67. Fagenholz PJ, Fuentes E, Kaafarani H, Cropano C, King D, de Moya M, et al. Computed Tomography Is More Sensitive than Ultrasound for the Diagnosis of Acute Cholecystitis. Surg Infect (Larchmt). 2015 Oct;16(5):509–12.
68. Hekimoglu K, Ustundag Y, Dusak A, Erdem Z, Karademir B, Aydemir S, et al. MRCP vs. ERCP in the evaluation of biliary pathologies: review of current literature. J Dig Dis. 2008 Aug;9(3):162–9.
69. Overby DW, Apelgren KN, Richardson W, Fanelli R. SAGES guidelines for the clinical application of laparoscopic biliary tract surgery. Surg Endosc. 2010 Oct;24(10):2368–86.
70. Gurusamy KKRFG, Davidson BR. Early versus delayed laparoscopic cholecystectomy for uncomplicated biliary colic. Cochrane Database of Systematic Reviews. John Wiley & Sons, Ltd; 2013;(6).
71. Wirth J, Song M, Fung TT, Joshi AD, Tabung FK, Chan AT, et al. Diet-quality scores and the risk of symptomatic gallstone disease: a prospective cohort study of male US health professionals. Int J Epidemiol. 2018 Dec;47(6):1938–46.
72. Schoenfield LJ, Lachin JM. Chenodiol (chenodeoxycholic acid) for dissolution of gallstones: the National Cooperative Gallstone

Study. A controlled trial of efficacy and safety. Ann Intern Med. 1981 Sep;95(3):257–82.
73. Petroni ML, Jazrawi RP, Pazzi P, Lanzini A, Zuin M, Pigozzi MG, et al. Ursodeoxycholic acid alone or with chenodeoxycholic acid for dissolution of cholesterol gallstones: a randomized multicentre trial. The British-Italian Gallstone Study group. Aliment Pharmacol Ther. 2001 Jan;15(1):123–8.
74. Janssen J, Johanns W, Weickert U, Rahmatian M, Greiner L. Long-term results after successful extracorporeal gallstone lithotripsy: outcome of the first 120 stone-free patients. Scand J Gastroenterol. 2001 Mar;36(3):314–7.
75. Shirah BH, Shirah HA, Zafar SH, Albeladi KB. Clinical patterns of postcholecystectomy syndrome. Ann Hepatobiliary Pancreat Surg. 2018 Feb;22(1):52–7.
76. Rehman S, Singh KK, Sajid MS. Role of laparoscopic cholecystectomy in the management of chronic right upper quadrant pain due to biliary dyskinesia: a systematic review and meta-analysis. Transl Gastroenterol Hepatol. 2019;4:71.
77. Gurusamy KS, Samraj K. Cholecystectomy versus no cholecystectomy in patients with silent gallstones. Cochrane Database Syst Rev. 2007 Jan;(1):CD006230.
78. Strom BL, Soloway RD, Rios-Dalenz JL, Rodriguez-Martinez HA, West SL, Kinman JL, et al. Risk factors for gallbladder cancer. An international collaborative case-control study. Cancer. 1995 Nov;76(10):1747–56.
79. Alli VV, Yang J, Xu J, Bates AT, Pryor AD, Talamini MA, et al. Nineteen-year trends in incidence and indications for laparoscopic cholecystectomy: the NY State experience. Surg Endosc. 2017 Apr;31(4):1651–8.
80. Friedman GD, Raviola CA, Fireman B. Prognosis of gallstones with mild or no symptoms: 25 years of follow-up in a health maintenance organization. J Clin Epidemiol. 1989;42(2):127–36.
81. Brazzelli M, Cruickshank M, Kilonzo M, Ahmed I, Stewart F, McNamee P, et al. Systematic review of the clinical and cost effectiveness of cholecystectomy versus observation/conservative management for uncomplicated symptomatic gallstones or cholecystitis. Surg Endosc. 2015 Mar;29(3):637–47.
82. Lee S, Chung C-W, Ko KH, Kwon SW. Risk factors for the clinical course of cholecystitis in patients who undergo cholecystectomy. Korean J Hepatobiliary Pancreat Surg. 2011 Aug;15(3):164–70.
83. Cho JY, Han H-S, Yoon Y-S, Ahn KS. Risk Factors for Acute Cholecystitis and a Complicated Clinical Course in Patients With Symptomatic Cholelithiasis. Arch Surg. 2010 Apr;145(4):329–33.
84. Loozen CS, van Ramshorst B, van Santvoort HC, Boerma D. Early Cholecystectomy for Acute Cholecystitis in the Elderly Population: A Systematic Review and Meta-Analysis. Dig Surg. 2017;34(5):371–9.
85. González-Castillo AM, Sancho-Insenser J, De Miguel-Palacio M, Morera-Casaponsa J-R, Membrilla-Fernández E, Pons-Fragero M-

J, et al. Mortality risk estimation in acute calculous cholecystitis: beyond the Tokyo Guidelines. World J Emerg Surg. 2021;16(1):24.
86. Pisano M, Allievi N, Gurusamy K, Borzellino G, Cimbanassi S, Boerna D, et al. 2020 World Society of Emergency Surgery updated guidelines for the diagnosis and treatment of acute calculus cholecystitis. World J Emerg Surg. 2020 Nov;15(1):61.
87. Yokoe M, Hata J, Takada T, Strasberg SM, Asbun HJ, Wakabayashi G, et al. Tokyo Guidelines 2018: diagnostic criteria and severity grading of acute cholecystitis (with videos). J Hepatobiliary Pancreat Sci. 2018 Jan;25(1):41–54.
88. Miura F, Okamoto K, Takada T, Strasberg SM, Asbun HJ, Pitt HA, et al. Tokyo Guidelines 2018: initial management of acute biliary infection and flowchart for acute cholangitis. J Hepatobiliary Pancreat Sci. 2018 Jan;25(1):31–40.
89. Sartelli M, Catena F, Ansaloni L, Coccolini F, Corbella D, Moore EE, et al. Complicated intra-abdominal infections worldwide: the definitive data of the CIAOW Study. World J Emerg Surg. 2014;9:37.
90. Wang A-J, Wang T-E, Lin C-C, Lin S-C, Shih S-C. Clinical predictors of severe gallbladder complications in acute acalculous cholecystitis. World J Gastroenterol. 2003 Dec;9(12):2821–3.
91. Trowbridge RL, Rutkowski NK, Shojania KG. Does this patient have acute cholecystitis? JAMA. 2003 Jan;289(1):80–6.
92. Naidu K, Beenen E, Gananadha S, Mosse C. The Yield of Fever, Inflammatory Markers and Ultrasound in the Diagnosis of Acute Cholecystitis: A Validation of the 2013 Tokyo Guidelines. World J Surg. 2016 Dec;40(12):2892–7.
93. Joseph B, Jehan F, Dacey M, Kulvatunyou N, Khan M, Zeeshan M, et al. Evaluating the Relevance of the 2013 Tokyo Guidelines for the Diagnosis and Management of Cholecystitis. J Am Coll Surg. 2018 Jul;227(1):38–43.e1.
94. Kiewiet JJS, Leeuwenburgh MMN, Bipat S, Bossuyt PMM, Stoker J, Boermeester MA. A systematic review and meta-analysis of diagnostic performance of imaging in acute cholecystitis. Radiology. 2012 Sep;264(3):708–20.
95. Ansaloni L, Pisano M, Coccolini F, Peitzmann AB, Fingerhut A, Catena F, et al. 2016 WSES guidelines on acute calculous cholecystitis. World J Emerg Surg. 2016;11:25.
96. Yeh DD, Cropano C, Fagenholz P, King DR, Chang Y, Klein EN, et al. Gangrenous cholecystitis: Deceiving ultrasounds, significant delay in surgical consult, and increased postoperative morbidity! J Trauma Acute Care Surg. 2015 Nov;79(5):812–6.
97. Fagenholz PJ, Fuentes E, Kaafarani H, Cropano C, King D, de Moya M, et al. Computed Tomography Is More Sensitive than Ultrasound for the Diagnosis of Acute Cholecystitis. Surg Infect (Larchmt). 2015 Oct;16(5):509–12.
98. Bates DDB, LeBedis CA, Soto JA, Gupta A. Use of Magnetic Resonance in Pancreaticobiliary Emergencies. Magn Reson Imaging Clin N Am. 2016 May;24(2):433–48.

99. de Mestral C, Rotstein OD, Laupacis A, Hoch JS, Zagorski B, Nathens AB. A population-based analysis of the clinical course of 10,304 patients with acute cholecystitis, discharged without cholecystectomy. J Trauma Acute Care Surg. 2013 Jan;74(1):26–30–discussion30–1.
100. Okamoto K, Suzuki K, Takada T, Strasberg SM, Asbun HJ, Endo I, et al. Tokyo Guidelines 2018: flowchart for the management of acute cholecystitis. J Hepatobiliary Pancreat Sci. 2018 Jan;25(1):55–72.
101. Gomi H, Solomkin JS, Schlossberg D, Okamoto K, Takada T, Strasberg SM, et al. Tokyo Guidelines 2018: antimicrobial therapy for acute cholangitis and cholecystitis. J Hepatobiliary Pancreat Sci. 2018 Jan;25(1):3–16.
102. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Intensive Care Med. 2017 Mar;43(3):304–77.
103. Endo I, Takada T, Hwang T-L, Akazawa K, Mori R, Miura F, et al. Optimal treatment strategy for acute cholecystitis based on predictive factors: Japan-Taiwan multicenter cohort study. J Hepatobiliary Pancreat Sci. 2017 Jun;24(6):346–61.
104. Yamashita Y, Takada T, Strasberg SM, Pitt HA, Gouma DJ, Garden OJ, et al. TG13 surgical management of acute cholecystitis. J Hepatobiliary Pancreat Sci. 2013 Jan;20(1):89–96.
105. Amirthalingam V, Low JK, Woon W, Shelat V. Tokyo Guidelines 2013 may be too restrictive and patients with moderate and severe acute cholecystitis can be managed by early cholecystectomy too. Surg Endosc. 2017 Jul;31(7):2892–900.
106. Peng WK, Sheikh Z, Paterson-Brown S, Nixon SJ. Role of liver function tests in predicting common bile duct stones in acute calculous cholecystitis. Br J Surg. 2005 Oct;92(10):1241–7.
107. Vettoretto N, Arezzo A, Famiglietti F, Cirocchi R, Moja L, Morino M. Laparoscopic-endoscopic rendezvous versus preoperative endoscopic sphincterotomy in people undergoing laparoscopic cholecystectomy for stones in the gallbladder and bile duct. Cochrane Database Syst Rev. 2018 Apr;4(4):CD010507.
108. Singh AN, Kilambi R. Single-stage laparoscopic common bile duct exploration and cholecystectomy versus two-stage endoscopic stone extraction followed by laparoscopic cholecystectomy for patients with gallbladder stones with common bile duct stones: systematic review and meta-analysis of randomized trials with trial sequential analysis. Surg Endosc. 2018 Sep;32(9):3763–76.
109. Lyu Y, Cheng Y, Li T, Cheng B, Jin X. Laparoscopic common bile duct exploration plus cholecystectomy versus endoscopic retrograde cholangiopancreatography plus laparoscopic cholecystectomy for cholecystocholedocholithiasis: a meta-analysis. Surg Endosc. 2019 Oct;33(10):3275–86.
110. de Mestral C, Rotstein OD, Laupacis A, Hoch JS, Zagorski B, Alali AS, et al. Comparative operative outcomes of early and delayed

cholecystectomy for acute cholecystitis: a population-based propensity score analysis. Ann Surg. 2014 Jan;259(1):10–5.
111. Song G-M, Bian W, Zeng X-T, Zhou J-G, Luo Y-Q, Tian X. Laparoscopic cholecystectomy for acute cholecystitis: early or delayed?: Evidence from a systematic review of discordant meta-analyses. Medicine (Baltimore). 2016 Jun;95(23):e3835.
112. Gurusamy KDCGC, Davidson BR. Early versus delayed laparoscopic cholecystectomy for people with acute cholecystitis. Cochrane Database of Systematic Reviews. John Wiley & Sons, Ltd; 2013;(6).
113. Borzellino G, Khuri S, Pisano M, Mansour S, Allievi N, Ansaloni L, et al. Timing of early laparoscopic cholecystectomy for acute calculous cholecystitis: a meta-analysis of randomized clinical trials. World J Emerg Surg. 2021 Mar;16(1):16.
114. Simopoulos C, Botaitis S, Polychronidis A, Tripsianis G, Karayiannakis AJ. Risk factors for conversion of laparoscopic cholecystectomy to open cholecystectomy. Surg Endosc. 2005 Jul;19(7):905–9.
115. Roulin D, Saadi A, Di Mare L, Demartines N, Halkic N. Early Versus Delayed Cholecystectomy for Acute Cholecystitis, Are the 72 hours Still the Rule?: A Randomized Trial. Ann Surg. 2016 Nov;264(5):717–22.
116. Gurusamy K, Samraj K, Gluud C, Wilson E, Davidson BR. Meta-analysis of randomized controlled trials on the safety and effectiveness of early versus delayed laparoscopic cholecystectomy for acute cholecystitis. Br J Surg. 2010 Feb;97(2):141–50.
117. Schmidt M, Søndenaa K, Vetrhus M, Berhane T, Eide GE. Long-term follow-up of a randomized controlled trial of observation versus surgery for acute cholecystitis: non-operative management is an option in some patients. Scand J Gastroenterol. 2011 Oct;46(10):1257–62.
118. Hatzidakis AA, Prassopoulos P, Petinarakis I, Sanidas E, Chrysos E, Chalkiadakis G, et al. Acute cholecystitis in high-risk patients: percutaneous cholecystostomy vs conservative treatment. Eur Radiol. 2002 Jul;12(7):1778–84.
119. Winbladh A, Gullstrand P, Svanvik J, Sandström P. Systematic review of cholecystostomy as a treatment option in acute cholecystitis. HPB (Oxford). 2009 May;11(3):183–93.
120. Loozen CS, van Santvoort HC, van Duijvendijk P, Besselink MG, Gouma DJ, Nieuwenhuijzen GA, et al. Laparoscopic cholecystectomy versus percutaneous catheter drainage for acute cholecystitis in high risk patients (CHOCOLATE): multicentre randomised clinical trial. BMJ. 2018 Oct;363:k3965.
121. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med. 1985 Oct;13(10):818–29.
122. Itoi T, Coelho-Prabhu N, Baron TH. Endoscopic gallbladder drainage for management of acute cholecystitis. Gastrointest Endosc. 2010 May;71(6):1038–45.

123. Itoi T, Kawakami H, Katanuma A, Irisawa A, Sofuni A, Itokawa F, et al. Endoscopic nasogallbladder tube or stent placement in acute cholecystitis: a preliminary prospective randomized trial in Japan (with videos). Gastrointest Endosc. 2015 Jan;81(1):111–8.
124. Khan MA, Atiq O, Kubiliun N, Ali B, Kamal F, Nollan R, et al. Efficacy and safety of endoscopic gallbladder drainage in acute cholecystitis: Is it better than percutaneous gallbladder drainage? Gastrointest Endosc. 2017 Jan;85(1):76–87.e3.
125. HURVITZ SA, AVERBOOK BD, HURVITZ RJ. Pancreatitis with Biliary Disease. Arch Surg. 1963 Apr;86(4):664–9.
126. Mirizzi PL. Sindrome del conduct hepatico. J Int Chir. 1948;(8):731–77.
127. Csendes A, Díaz JC, Burdiles P, Maluenda F, Nava O. Mirizzi syndrome and cholecystobiliary fistula: a unifying classification. Br J Surg. 1989 Nov;76(11):1139–43.
128. Langenbuch C. Ein Fall von Exstirpation der Gallenblase wegen Chronisher Cholelithisip. Heilung. Berliner Klinische Wochenschrift. 1882;(19):725.
129. Senra F, Navaratne L, Acosta A, Martínez-Isla A. Laparoscopic management of type II Mirizzi syndrome. Surg Endosc. 2020 May;34(5):2303–12.
130. Mühe E. [Laparoscopic cholecystectomy--late results]. Langenbecks Arch Chir Suppl Kongressbd. 1991;:416–23.
131. Kramp KH, van Det MJ, Totte ER, Hoff C, Pierie J-PEN. Ergonomic assessment of the French and American position for laparoscopic cholecystectomy in the MIS Suite. Surg Endosc. 2014 May;28(5):1571–8.
132. Brunt LM, Deziel DJ, Telem DA, Strasberg SM, Aggarwal R, Asbun H, et al. Safe Cholecystectomy Multi-society Practice Guideline and State of the Art Consensus Conference on Prevention of Bile Duct Injury During Cholecystectomy. Ann Surg. 2020 Jul;272(1):3–23.
133. Woodfield JC, Rodgers M, Windsor JA. Peritoneal gallstones following laparoscopic cholecystectomy: incidence, complications, and management. Surg Endosc. 2004 Aug;18(8):1200–7.
134. Sanabria A, Dominguez LC, Valdivieso E, Gomez G. Antibiotic prophylaxis for patients undergoing elective laparoscopic cholecystectomy. Cochrane Database Syst Rev. 2010 Dec;(12):CD005265.
135. Sajid MS, Bovis J, Rehman S, Singh KK. Prophylactic antibiotics at the time of elective cholecystectomy are effective in reducing the post-operative infective complications: a systematic review and meta-analysis. Transl Gastroenterol Hepatol. 2018;3:22.
136. Rice DC, Memon MA, Jamison RL, Agnessi T, Ilstrup D, Bannon MB, et al. Long-term consequences of intraoperative spillage of bile and gallstones during laparoscopic cholecystectomy. J Gastrointest Surg. 1997 Jan;1(1):85–90–discussion90–1.
137. Guzmán-Valdivia G. Routine administration of antibiotics to patients suffering accidental gallbladder perforation during

laparoscopic cholecystectomy is not necessary. Surg Laparosc Endosc Percutan Tech. 2008 Dec;18(6):547–50.
138. Steiner CA, Bass EB, Talamini MA, Pitt HA, Steinberg EP. Surgical rates and operative mortality for open and laparoscopic cholecystectomy in Maryland. N Engl J Med. 1994 Feb;330(6):403–8.
139. Talseth A, Lydersen S, Skjedlestad F, Hveem K, Edna T-H. Trends in cholecystectomy rates in a defined population during and after the period of transition from open to laparoscopic surgery. Scand J Gastroenterol. 2014 Jan;49(1):92–8.
140. Koppatz H, Harju J, Sirén J, Mentula P, Scheinin T, Sallinen V. Three-dimensional versus two-dimensional high-definition laparoscopy in cholecystectomy: a prospective randomized controlled study. Surg Endosc. 2019 Nov;33(11):3725–31.
141. Schwab KE, Curtis NJ, Whyte MB, Smith RV, Rockall TA, Ballard K, et al. 3D laparoscopy does not reduce operative duration or errors in day-case laparoscopic cholecystectomy: a randomised controlled trial. Surg Endosc. 2020 Apr;34(4):1745–53.
142. Davidoff AM, Pappas TN, Murray EA, Hilleren DJ, Johnson RD, Baker ME, et al. Mechanisms of major biliary injury during laparoscopic cholecystectomy. Ann Surg. 1992 Mar;215(3):196–202.
143. Morgenstern L, Wong L, Berci G. Twelve hundred open cholecystectomies before the laparoscopic era. A standard for comparison. Arch Surg. 1992 Apr;127(4):400–3.
144. Halbert C, Pagkratis S, Yang J, Meng Z, Altieri MS, Parikh P, et al. Beyond the learning curve: incidence of bile duct injuries following laparoscopic cholecystectomy normalize to open in the modern era. Surg Endosc. 2016 Jun;30(6):2239–43.
145. O'Brien S, Wei D, Bhutiani N, Rao MK, Johnston SS, Patkar A, et al. Adverse outcomes and short-term cost implications of bile duct injury during cholecystectomy. Surg Endosc. 2020 Feb;34(2):628–35.
146. Tsalis K, Antoniou N, Koukouritaki Z, Patridas D, Christoforidis E, Lazaridis C. Open-access technique and “critical view of safety” as the safest way to perform laparoscopic cholecystectomy. Surg Laparosc Endosc Percutan Tech. 2015 Apr;25(2):119–24.
147. Strasberg SM, Brunt LM. Rationale and use of the critical view of safety in laparoscopic cholecystectomy. J Am Coll Surg. 2010 Jul;211(1):132–8.
148. Way LW, Stewart L, Gantert W, Liu K, Lee CM, Whang K, et al. Causes and prevention of laparoscopic bile duct injuries: analysis of 252 cases from a human factors and cognitive psychology perspective. Ann Surg. 2003 Apr;237(4):460–9.
149. Strasberg SM, Eagon CJ, Drebin JA. The “hidden cystic duct” syndrome and the infundibular technique of laparoscopic cholecystectomy--the danger of the false infundibulum. J Am Coll Surg. 2000 Dec;191(6):661–7.

150. Strasberg SM, Gouma DJ. “Extreme” vasculobiliary injuries: association with fundus-down cholecystectomy in severely inflamed gallbladders. HPB (Oxford). 2012 Jan;14(1):1–8.
151. Thomson BNJ, Cullinan MJ, Banting SW, Collier NA. Recognition and management of biliary complications after laparoscopic cholecystectomy. ANZ J Surg. 2003 Apr;73(4):183–8.
152. Olsen D. Bile duct injuries during laparoscopic cholecystectomy. Surg Endosc. 1997 Feb;11(2):133–8.
153. Carroll BJ, Birth M, Phillips EH. Common bile duct injuries during laparoscopic cholecystectomy that result in litigation. Surg Endosc. 1998 Apr;12(4):310–3–discussion314.
154. Fletcher DR, Hobbs MS, Tan P, Valinsky LJ, Hockey RL, Pikora TJ, et al. Complications of cholecystectomy: risks of the laparoscopic approach and protective effects of operative cholangiography: a population-based study. Ann Surg. 1999 Apr;229(4):449–57.
155. Tornqvist B, Stromberg C, Persson G, Nilsson M. Effect of intended intraoperative cholangiography and early detection of bile duct injury on survival after cholecystectomy: population based cohort study. BMJ. 2012;345:e6457.
156. Rystedt JML, Wiss J, Adolfsson J, Enochsson L, Hallerbäck B, Johansson P, et al. Routine versus selective intraoperative cholangiography during cholecystectomy: systematic review, meta-analysis and health economic model analysis of iatrogenic bile duct injury. BJS Open. 2021 Mar;5(2).
157. Sanjay P, Tagolao S, Dirkzwager I, Bartlett A. A survey of the accuracy of interpretation of intraoperative cholangiograms. HPB (Oxford). 2012 Oct;14(10):673–6.
158. Jamal KN, Smith H, Ratnasingham K, Siddiqui MR, McLachlan G, Belgaumkar AP. Meta-analysis of the diagnostic accuracy of laparoscopic ultrasonography and intraoperative cholangiography in detection of common bile duct stones. Ann R Coll Surg Engl. 2016 Apr;98(4):244–9.
159. Dip F, LoMenzo E, Sarotto L, Phillips E, Todeschini H, Nahmod M, et al. Randomized Trial of Near-infrared Incisionless Fluorescent Cholangiography. Ann Surg. 2019 Dec;270(6):992–9.
160. Quaresima S, Balla A, Palmieri L, Seitaj A, Fingerhut A, Ursi P, et al. Routine near infra-red indocyanine green fluorescent cholangiography versus intraoperative cholangiography during laparoscopic cholecystectomy: a case-matched comparison. Surg Endosc. 2020 May;34(5):1959–67.
161. Eldar S, Sabo E, Nash E, Abrahamson J, Matter I. Laparoscopic cholecystectomy for acute cholecystitis: prospective trial. World J Surg. 1997 Jun;21(5):540–5.
162. Yang TF, Guo L, Wang Q. Evaluation of Preoperative Risk Factor for Converting Laparoscopic to Open Cholecystectomy: A Meta-Analysis. Hepatogastroenterology. 2014 Jun;61(132):958–65.
163. Philip Rothman J, Burcharth J, Pommergaard H-C, Viereck S, Rosenberg J. Preoperative Risk Factors for Conversion of Laparoscopic Cholecystectomy to Open Surgery - A Systematic

Review and Meta-Analysis of Observational Studies. Dig Surg. 2016;33(5):414–23.
164. Bornman PC, Terblanche J. Subtotal cholecystectomy: for the difficult gallbladder in portal hypertension and cholecystitis. Surgery. 1985 Jul;98(1):1–6.
165. Bickel A, Shtamler B. Laparoscopic subtotal cholecystectomy. J Laparoendosc Surg. 1993 Aug;3(4):365–7.
166. Henneman D, da Costa DW, Vrouenraets BC, van Wagensveld BA, Lagarde SM. Laparoscopic partial cholecystectomy for the difficult gallbladder: a systematic review. Surg Endosc. 2013 Feb;27(2):351–8.
167. Elshaer M, Gravante G, Thomas K, Sorge R, Al-Hamali S, Ebdewi H. Subtotal cholecystectomy for "difficult gallbladders": systematic review and meta-analysis. JAMA Surg. 2015 Feb;150(2):159–68.
168. Lidsky ME, Speicher PJ, Ezekian B, Holt EW, Nussbaum DP, Castleberry AW, et al. Subtotal cholecystectomy for the hostile gallbladder: failure to control the cystic duct results in significant morbidity. HPB (Oxford). 2017;19(6):547–56.
169. Hubert C, Annet L, van Beers BE, Gigot J-F. The "inside approach of the gallbladder" is an alternative to the classic Calot's triangle dissection for a safe operation in severe cholecystitis. Surg Endosc. 2010 Oct;24(10):2626–32.
170. Singhal T, Balakrishnan S, Hussain A, Nicholls J, Grandy-Smith S, El-Hasani S. Laparoscopic subtotal cholecystectomy: initial experience with laparoscopic management of difficult cholecystitis. Surgeon. 2009 Oct;7(5):263–8.
171. Enochsson L, Thulin A, Osterberg J, Sandblom G, Persson G. The Swedish Registry of Gallstone Surgery and Endoscopic Retrograde Cholangiopancreatography (GallRiks): A nationwide registry for quality assurance of gallstone surgery. JAMA Surg. 2013 May;148(5):471–8.
172. Burke J, Rattan R, Sedighim S, Kim M. A Simple Risk Score to Predict Clavien-Dindo Grade IV and V Complications After Non-elective Cholecystectomy. J Gastrointest Surg. 2021 Jan;25(1):201–10.
173. Carbonell AM, Lincourt AE, Kercher KW, Matthews BD, Cobb WS, Sing RF, et al. Do patient or hospital demographics predict cholecystectomy outcomes? A nationwide study of 93,578 patients. Surg Endosc. 2005 Jun;19(6):767–73.
174. Su CH, P'eng FK, Lui WY. Factors affecting morbidity and mortality in biliary tract surgery. World J Surg. 1992 May;16(3):536–40.
175. Ausania F, Guzman Suarez S, Alvarez Garcia H, Senra del Rio P, Casal Nuñez E. Gallbladder perforation: morbidity, mortality and preoperative risk prediction. Surg Endosc. 2015 Apr;29(4):955–60.
176. Rosenmüller M, Haapamäki MM, Nordin P, Stenlund H, Nilsson E. Cholecystectomy in Sweden 2000 – 2003: a nationwide study on procedures, patient characteristics, and mortality. BMC Gastroenterol. 2007;7:35.

177. Sandblom G, Videhult P, Crona Guterstam Y, Svenner A, Sadr-Azodi O. Mortality after a cholecystectomy: a population-based study. HPB (Oxford). 2015 Mar;17(3):239–43.
178. Suuronen S, Kivivuori A, Tuimala J, Paajanen H. Bleeding complications in cholecystectomy: a register study of over 22,000 cholecystectomies in Finland. BMC Surg. 2015 Aug;15:97.
179. Schäfer M, Lauper M, Krähenbühl L. A nation's experience of bleeding complications during laparoscopy. Am J Surg. 2000 Jul;180(1):73–7.
180. Opitz I, Gantert W, Giger U, Kocher T, Krahenbuhl L. Bleeding remains a major complication during laparoscopic surgery: analysis of the SALTS database. Langenbecks Arch Surg. 2005 Apr;390(2):128–33.
181. Pulvirenti E, Toro A, Gagner M, Mannino M, Di Carlo I. Increased rate of cholecystectomies performed with doubtful or no indications after laparoscopy introduction: a single center experience. BMC Surg. 2013 May;13:17.
182. Nordin A, Halme L, Mäkisalo H, Isoniemi H, Höckerstedt K. Management and outcome of major bile duct injuries after laparoscopic cholecystectomy: from therapeutic endoscopy to liver transplantation. Liver Transpl. 2002 Nov;8(11):1036–43.
183. Koppatz H, Sallinen V, Mäkisalo H, Nordin A. Outcomes and quality of life after major bile duct injury in long-term follow-up. Surg Endosc. 2020 Jun.
184. Cho JY, Baron TH, Carr-Locke DL, Chapman WC, Costamagna G, de Santibanes E, et al. Proposed standards for reporting outcomes of treating biliary injuries. HPB (Oxford). Elsevier; 2018 Apr 1;20(4):370–8.
185. Arcerito M, Jamal MM, Nurick HA. Bile Duct Injury Repairs after Laparoscopic Cholecystectomy: A Five-Year Experience in a Highly Specialized Community Hospital. Am Surg. 2019 Oct;85(10):1150–4.
186. Lim DZ, Wong E, Hassen S, Al-Habbal Y. Retroperitoneal bile leak after laparoscopic cholecystectomy. BMJ Case Rep. 2018 Jan;2018.
187. Li J, Frilling A, Nadalin S, Paul A, Malagò M, Broelsch CE. Management of concomitant hepatic artery injury in patients with iatrogenic major bile duct injury after laparoscopic cholecystectomy. Br J Surg. 2008 Apr;95(4):460–5.
188. Halasz NA. Cholecystectomy and hepatic artery injuries. Arch Surg. 1991 Feb;126(2):137–8.
189. Bacha EA, Stieber AC, Galloway JR, Hunter JG. Non-biliary complication of laparoscopic cholecystectomy. Lancet. 1994 Sep;344(8926):896–7.
190. Kaman L, Sanyal S, Behera A, Singh R, Katariya RN. Comparison of major bile duct injuries following laparoscopic cholecystectomy and open cholecystectomy. ANZ J Surg. 2006 Sep;76(9):788–91.
191. Lien H-H, Huang C-C, Liu J-S, Shi M-Y, Chen D-F, Wang N-Y, et al. System approach to prevent common bile duct injury and

enhance performance of laparoscopic cholecystectomy. Surg Laparosc Endosc Percutan Tech. 2007 Jun;17(3):164–70.
192. Francoeur JR, Wiseman K, Buczkowski AK, Chung SW, Scudamore CH. Surgeons' anonymous response after bile duct injury during cholecystectomy. Am J Surg. 2003 May;185(5):468–75.
193. OTI-vuosiraportti 2019.
194. Eisenstein S, Greenstein AJ, Kim U, Divino CM. Cystic duct stump leaks: after the learning curve. Arch Surg. 2008 Dec;143(12):1178–83.
195. Lillemoe KD, Petrofski JA, Choti MA, Venbrux AC, Cameron JL. Isolated right segmental hepatic duct injury: a diagnostic and therapeutic challenge. J Gastrointest Surg. 2000 Mar;4(2):168–77.
196. Schreuder AM, Busch OR, Besselink MG, Ignatavicius P, Gulbinas A, Barauskas G, et al. Long-Term Impact of Iatrogenic Bile Duct Injury. Dig Surg. 2020;37(1):10–21.
197. Stewart L, Way LW. Bile duct injuries during laparoscopic cholecystectomy. Factors that influence the results of treatment. Arch Surg. 1995 Oct;130(10):1123–8–discussion1129.
198. Schreuder AM, Nunez Vas BC, Booij KAC, van Dieren S, Besselink MG, Busch OR, et al. Optimal timing for surgical reconstruction of bile duct injury: meta-analysis. BJS Open. 2020 Oct;4(5):776–86.
199. Pickleman J, Marsan R, Borge M. Portoenterostomy: an old treatment for a new disease. Arch Surg. 2000 Jul;135(7):811–7.
200. Kasai M, Kimura S, Asakura Y, Suzuki H, Taira Y, Ohashi E. Surgical treatment of biliary atresia. Journal of Pediatric Surgery. 1968;3(6):665–75.
201. Robertson AJ, Rela M, Karani J, Steger AC, Benjamin IS, Heaton ND. Laparoscopic cholecystectomy injury: an unusual indication for liver transplantation. Transpl Int. 1998;11(6):449–51.
202. Flum DR, Cheadle A, Prela C, Dellinger EP, Chan L. Bile duct injury during cholecystectomy and survival in medicare beneficiaries. JAMA. 2003 Oct;290(16):2168–73.
203. Suuronen S, Koski A, Nordstrom P, Miettinen P, Paajanen H. Laparoscopic and open cholecystectomy in surgical training. Dig Surg. 2010;27(5):384–90.
204. Chung RS. How much time do surgical residents need to learn operative surgery? Am J Surg. 2005 Sep;190(3):351–3.
205. Whewell H, Brown C, Gokani VJ, Harries RL, Aguilera ML, Ahrend H, et al. Variation in training requirements within general surgery: comparison of 23 countries. BJS Open. 2020 Aug;4(4):714–23.
206. Shubeck SP, Kanters AE, Dimick JB. Surgeon leadership style and risk-adjusted patient outcomes. Surg Endosc. 2019 Feb;33(2):471–4.
207. Ericsson K, Krampe R, Tesch-Roemer C. The Role of Deliberate Practice in the Acquisition of Expert Performance. Psychological Review. 1993 Jul;100:363–406.
208. Esserman L, Cowley H, Eberle C, Kirkpatrick A, Chang S, Berbaum K, et al. Improving the Accuracy of Mammography: Volume and

Outcome Relationships. JNCI: Journal of the National Cancer Institute. 2002 Mar;94(5):369–75.
209. Portelli M, Bianco SF, Bezzina T, Abela JE. Virtual reality training compared with apprenticeship training in laparoscopic surgery: a meta-analysis. Ann R Coll Surg Engl. 2020 Nov;102(9):672–84.
210. Dawe SR, Windsor JA, Broeders JAJL, Cregan PC, Hewett PJ, Maddern GJ. A systematic review of surgical skills transfer after simulation-based training: laparoscopic cholecystectomy and endoscopy. Ann Surg. 2014 Feb;259(2):236–48.
211. Chowdhury MM, Dagash H, Pierro A. A systematic review of the impact of volume of surgery and specialization on patient outcome. Br J Surg. 2007 Feb;94(2):145–61.
212. Modrall JG, Minter RM, Minhajuddin A, Eslava-Schmalbach J, Joshi GP, Patel S, et al. The Surgeon Volume-outcome Relationship: Not Yet Ready for Policy. Ann Surg. 2018 May;267(5):863–7.
213. Nordback L, Parviainen M, Räty S, Kuivanen H, Sand J. Resection of the head of the pancreas in Finland: effects of hospital and surgeon on short-term and long-term results. Scand J Gastroenterol. 2002 Dec;37(12):1454–60.
214. de Wilde RF, Besselink MGH, van der Tweel I, de Hingh IHJT, van Eijck CHJ, Dejong CHC, et al. Impact of nationwide centralization of pancreaticoduodenectomy on hospital mortality. Br J Surg. 2012 Mar;99(3):404–10.
215. Andrews S. Does concentration of surgical expertise improve outcomes for laparoscopic cholecystectomy? 9 year audit cycle. Surgeon. 2013 Dec;11(6):309–12.
216. Abelson JS, Spiegel JD, Afaneh C, Mao J, Sedrakyan A, Yeo HL. Evaluating cumulative and annual surgeon volume in laparoscopic cholecystectomy. Surgery. 2017 Mar;161(3):611–7.
217. Harrison EM, O'Neill S, Meurs TS, Wong PL, Duxbury M, Paterson-Brown S, et al. Hospital volume and patient outcomes after cholecystectomy in Scotland: retrospective, national population based study. BMJ. 2012 May;344:e3330.
218. Sinha S, Hofman D, Stoker DL, Friend PJ, Poloniecki JD, Thompson MM, et al. Epidemiological study of provision of cholecystectomy in England from 2000 to 2009: retrospective analysis of Hospital Episode Statistics. Surg Endosc. 2013 Jan;27(1):162–75.
219. Murphy MM, Ng S-C, Simons JP, Csikesz NG, Shah SA, Tseng JF. Predictors of Major Complications after Laparoscopic Cholecystectomy: Surgeon, Hospital, or Patient? J Am Coll Surg. 2010;211(1):73–80.
220. Donkervoort SC, Dijksman LM, Versluis PG, Clous EA, Vahl AC. Surgeon's volume is not associated with complication outcome after laparoscopic cholecystectomy. Dig Dis Sci. 2014 Jan;59(1):39–45.
221. Csikesz NG, Singla A, Murphy MM, Tseng JF, Shah SA. Surgeon volume metrics in laparoscopic cholecystectomy. Dig Dis Sci. 2010 Aug;55(8):2398–405.

222. Kortram K, Reinders JSK, van Ramshorst B, Wiezer MJ, Go PMNYH, Boerma D. Laparoscopic cholecystectomy for acute cholecystitis should be performed by a laparoscopic surgeon. Surg Endosc. 2010 Sep;24(9):2206–9.
223. Dindo D, Demartines N, Clavien P-A. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004 Aug;240(2):205–13.
224. Slankamenac K, Graf R, Barkun J, Puhan MA, Clavien P-A. The comprehensive complication index: a novel continuous scale to measure surgical morbidity. Ann Surg. 2013 Jul;258(1):1–7.
225. Sanford DE, Strasberg SM. A simple effective method for generation of a permanent record of the Critical View of Safety during laparoscopic cholecystectomy by intraoperative "doublet" photography. J Am Coll Surg. 2014 Feb;218(2):170–8.
226. Spiegelhalter DJ. Funnel plots for comparing institutional performance. Statistics in Medicine. John Wiley & Sons, Ltd; 2005;24(8):1185–202.
227. Onoe S, Maeda A, Takayama Y, Fukami Y, Kaneoka Y. A preoperative predictive scoring system to predict the ability to achieve the critical view of safety during laparoscopic cholecystectomy for acute cholecystitis. HPB (Oxford). 2017 May;19(5):406–10.
228. Bourikian S, Anand RJ, Aboutanos M, Wolfe LG, Ferrada P. Risk factors for acute gangrenous cholecystitis in emergency general surgery patients. Am J Surg. 2015;210(4):730–3.
229. Ambe PC, Köhler L. Is the male gender an independent risk factor for complication in patients undergoing laparoscopic cholecystectomy for acute cholecystitis? Int Surg. 2015 May;100(5):854–9.
230. Zdichavsky M, Bashin YA, Blumenstock G, Zieker D, Meile T, Konigsrainer A. Impact of risk factors for prolonged operative time in laparoscopic cholecystectomy. Eur J Gastroenterol Hepatol. 2012 Sep;24(9):1033–8.
231. Inoue K, Ueno T, Douchi D, Shima K, Goto S, Takahashi M, et al. Risk factors for difficulty of laparoscopic cholecystectomy in grade II acute cholecystitis according to the Tokyo guidelines 2013. BMC Surg. 2017 Nov;17(1):114.
232. Lucocq J, Scollay J, Patil P. Elective laparoscopic cholecystectomy: recurrent biliary admissions predispose to difficult cholecystectomy. Surg Endosc. 2022 Jan.
233. Meyer CP, Rios-Diaz AJ, Dalela D, Ravi P, Sood A, Hanske J, et al. The association of hypoalbuminemia with early perioperative outcomes - A comprehensive assessment across 16 major procedures. Am J Surg. 2017 Nov;214(5):871–83.
234. Human albumin solution for resuscitation and volume expansion in critically ill patients. Cochrane Database Syst Rev. 2011 Oct;(10):CD001208.

235. Brown C, Abdelrahman T, Patel N, Thomas C, Pollitt MJ, Lewis WG. Operative learning curve trajectory in a cohort of surgical trainees. Br J Surg. 2017 Sep;104(10):1405–11.
236. Csikesz NG, Singla A, Murphy MM, Tseng JF, Shah SA. Surgeon volume metrics in laparoscopic cholecystectomy. Dig Dis Sci. 2010 Aug;55(8):2398–405.
237. Hobbs MS, Mai Q, Knuiman MW, Fletcher DR, Ridout SC. Surgeon experience and trends in intraoperative complications in laparoscopic cholecystectomy. Br J Surg. 2006 Jul;93(7):844–53.
238. Davidoff AM, Pappas TN, Murray EA, Hilleren DJ, Johnson RD, Baker ME, et al. Mechanisms of major biliary injury during laparoscopic cholecystectomy. Ann Surg. 1992 Mar;215(3):196–202.
239. Roethlisberger FJ, Dickson WJ. Management and the worker. Oxford, England: Harvard Univ. Press SN ; 1939. 3 p.
240. Augestad KM, Butt K, Ignjatovic D, Keller DS, Kiran R. Video-based coaching in surgical education: a systematic review and meta-analysis. Surg Endosc. 2020 Feb;34(2):521–35.
241. Nijssen MAJ, Schreinemakers JMJ, Meyer Z, van der Schelling GP, Crolla RMPH, Rijken AM. Complications After Laparoscopic Cholecystectomy: A Video Evaluation Study of Whether the Critical View of Safety was Reached. World J Surg. 2015 Jul;39(7):1798–803.
242. Iskandar M, Fingerhut A, Ferzli G. Posterior infundibular dissection: safety first in laparoscopic cholecystectomy. Surg Endosc. 2021 Jun;35(6):3175–83.