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IATROGENIC BILE DUCT INJURY DURING CHOLECYSTECTOMY

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Stockholm 2013

Published by Karolinska Institutet. Printed by Universitetsservice AB

ISBN 978-91-7549-220-9

To Annelie, Linnéa and Olivia

“Die Kontroversen über die Cholelithiasis sind, trotz der über diesen Gegenstand vorliegenden, fast unübersehbaren Litteratur, noch weit davon entfernt, endgultig abgeschlossen zu sein. Denn wenn letzteres zwar in gewisser Beziehung von der Symptomatologie und von der Kenntnis der Genese der Steine gesagt werden darf, so sind immerhin innerhalb der Bakteriologie, der pathologischen Anatomie und der Behandlungsweise der Krankheit noch genug Punkte vorhanden, die einer auf fortgesetzte Beobachtungen gestützten Aufklärung harren.”

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“The controversies over cholelithiasis remain far from being definitively settled, despite the evident literature available on the subject. Whilst this may not apply, in some respects, to the symptomatology and the knowledge of gallstone genesis, there nonetheless continues to exist sufficient points within the bacteriology, the pathologic anatomy and the treatment of the condition that await clarification, warranted by continuous observations.”

Beiträge zur Pathologie und Therapie der Gallsteinkrankenheit

(Contributions to the Pathology and Therapy of Gallstone disease)

Von

G.W. TÖRNQVIST

Stockholm 1903

(Author‘s great grandfather)

”I will not cut for stone, even for patients in whom the disease is manifest; I will leave this operation to be performed by practitioners, specialists in this art.”

The Hippocratic oath (460 BC – 377 BC)

ABSTRACT

Background: Accidental injuries to the bile ducts are a rare but devastating complication to cholecystectomy, causing afflicted patients considerable morbidity, with subsequent impaired quality of life and significant health related costs. The knowledge regarding incidence, morbidity and prevention of such injuries is limited.
Objectives: To investigate the incidence of bile duct injuries (BDI) in Sweden. To evaluate the long-term morbidity pattern after BDI. To estimate the mortality rate and factors associated with increased mortality following BDI. To address prevention of BDI by the identification of risk factors and evaluation of the possible protective effect by intraoperative cholangiography (IOC).
Methods: In study I, all cholecystectomies within the Swedish Inpatient Registry between 1965 and 2005 were included. BDI were identified through International Classification of Diseases (ICD) procedure codes, pertaining to surgical reconstruction of the bile ducts, and analysed for survival, factors influencing the survival and causes of death. In study II and III, all cholecystectomies within the Swedish Registry for Gallstone Surgery, GallRiks, between 2005 and 2010, were analysed for BDI. Analyses regarding incidence, survival and risk factors for BDI were performed using multivariable Cox (Study II) and logistic regression (Study III) models. Study IV is a nested, matched case-control study of BDI patients (cases) and non-injured cholecystectomies (controls). After a review of medical records, multivariable logistic regression models were used to investigate the association between different severity-grades of acute cholecystitis and BDI.
Results: In study I, 374 042 cholecystectomised patients were identified, of which 1 386 had reconstructed BDI. Survival was significantly lower in the injured group, with a hazard ratio of 3.73 at year one, which thereafter gradually evened out. The risk of dying from liver diseases was four-fold increased in the BDI cohort compared to the general population. In study II, 51041 cholecystectomies and 747 (1.46%) BDI were identified, ranging from minor to major injuries. Injured patients had an impaired survival compared to non-injured but early detection of BDI, during the primary operation, improved survival. The intention to use IOC reduced the risk of dying after cholecystectomy by 62% and reduced BDI rates by 29%. In study III, increased age, comorbidity and on-going or a history of acute cholecystitis were independent risk factors of BDI. Among patients with acute cholecystitis, the intention to use IOC reduced BDI risk by 66%. For patients with a history of acute cholecystitis, the equivalent reduction in risk was 41%. Among patients with uncomplicated gallstone disease, no preventive effect of IOC was seen. In study IV, 158 BDI and 623 controls were analysed. Mild acute cholecystitis did not increase the risk of BDI whereas moderate and severe forms gradually increased BDI risk.
Conclusions: BDI is more common than previously reported, with reduced short and long term survival, partly due to an overrepresentation of liver related diseases. Increasing age, comorbidity and moderate to severe inflammatory changes of the gallbladder are important risk factors for BDI. The intentional use of IOC reduced BDI rates and improves survival after cholecystectomy. As the protective effect of IOC seems to be confined to patients with, or with a history of acute cholecystitis, routine IOC should be recommended within this group whereas a selective IOC approach among uncomplicated gallstone disease is likewise safe.

LIST OF PUBLICATIONS

The thesis is based on the following papers, which will be referred to by their roman numerals:

I. Björn Törnqvist, Zongli Zheng, Weimin Ye, Anne Waage and Magnus Nilsson
Long-term effects of iatrogenic bile duct injury during cholecystectomy
Clinical Gastroenterology and Hepatology, 2009, 7, 1013-1018

II. Björn Törnqvist, Cecilia Strömberg, Gunnar Persson and Magnus Nilsson
Effect of intended intraoperative cholangiography and early detection of bile duct injury on survival after cholecystectomy: population based cohort study
British Medical Journal, 2012, 345, e6457

III. Björn Törnqvist, Cecilia Strömberg, Olof Akre, Lars Enochsson and Magnus Nilsson
Risk factors for iatrogenic bile duct injury during cholecystectomy, Swedish national registry data
Submitted manuscript

IV. Björn Törnqvist, Anne Waage, Zongli Zheng, Weimin Ye and Magnus Nilsson
Severity of acute cholecystitis and risk of iatrogenic bile duct injury during cholecystectomy, a population based case-control study
Submitted manuscript

CONTENTS

LIST OF ABBREVIATIONS

ASA	American Association of Anesthesiologists
BDI	Bile Duct Injury
BMI	Body Mass Index
CBD	Common Bile Duct
CBDS	Common Bile Duct Stones
CHD	Common Hepatic Duct
CI	Confidence Interval
CRP	C-Reactive Protein
CT	Computed Tomography
ERC	Endoscopic Retrograde Cholangiography
ERCP	Endoscopic Retrograde Cholangiopancreatography
HR	Hazard Ratio
ICD	International Classification of Diseases
IOC	Intraoperative Cholangiography
MRCP	Magnetic Resonance Cholangiopancreatography
MRI	Magnetic Resonance Imaging
OR	Odds Ratio
PTC	Percutaneous Transhepatic Cholangiography
QOL	Quality Of Life
RCT	Randomized Controlled Trial
ROC	Receiver Operating Characteristic
SIR	Standardized Incidence Ratio
SMR	Standardized Mortality Ratio
TG13	Tokyo Guidelines 2013
WBC	White Blood Cell
WHO	World Health Organization

1 INTRODUCTION

Cholecystectomy due to gallstones is one of the most common surgical procedures and is considered a routine operation in modern surgery. Although a routine procedure, the consequences of accidental injuries to the bile ducts may have a severe impact on health of afflicted patients, including mortality and considerable disability, and poses a major economic burden both to the individual patient and to the health care system at large[1-4].

The knowledge about incidence, morbidity and prevention of iatrogenic bile duct injury (BDI) is limited. A majority of research is based on single centre experiences, usually presenting low morbidity and almost negligible mortality. These findings sharply contrast the results of the few larger population based studies reporting devastating morbidity and mortality figures almost resembling those of malignant disease[2]. The relative paucity of BDI precludes research based on randomized controlled trials due to the massive sample sizes needed to obtain sufficient power. Epidemiological methods allow for studies of rare outcomes, but valid and conclusive research concerning risk factors and survival after BDI is scarce.

This thesis, based on four original papers, aims at a better understanding of the incidence, consequences and prevention of BDI. Accurate estimations of BDI incidence is of fundamental importance for analyses of the impact on patients' health, treatment outcome and costs. A thorough knowledge of morbidity and mortality after BDI is a prerequisite for optimal treatment and follow-up. By identifying risk factors and assessment of optimal surgical techniques, we can provide a scientific basis for effective primary prevention, thereby reducing the devastating consequences of iatrogenic BDI.

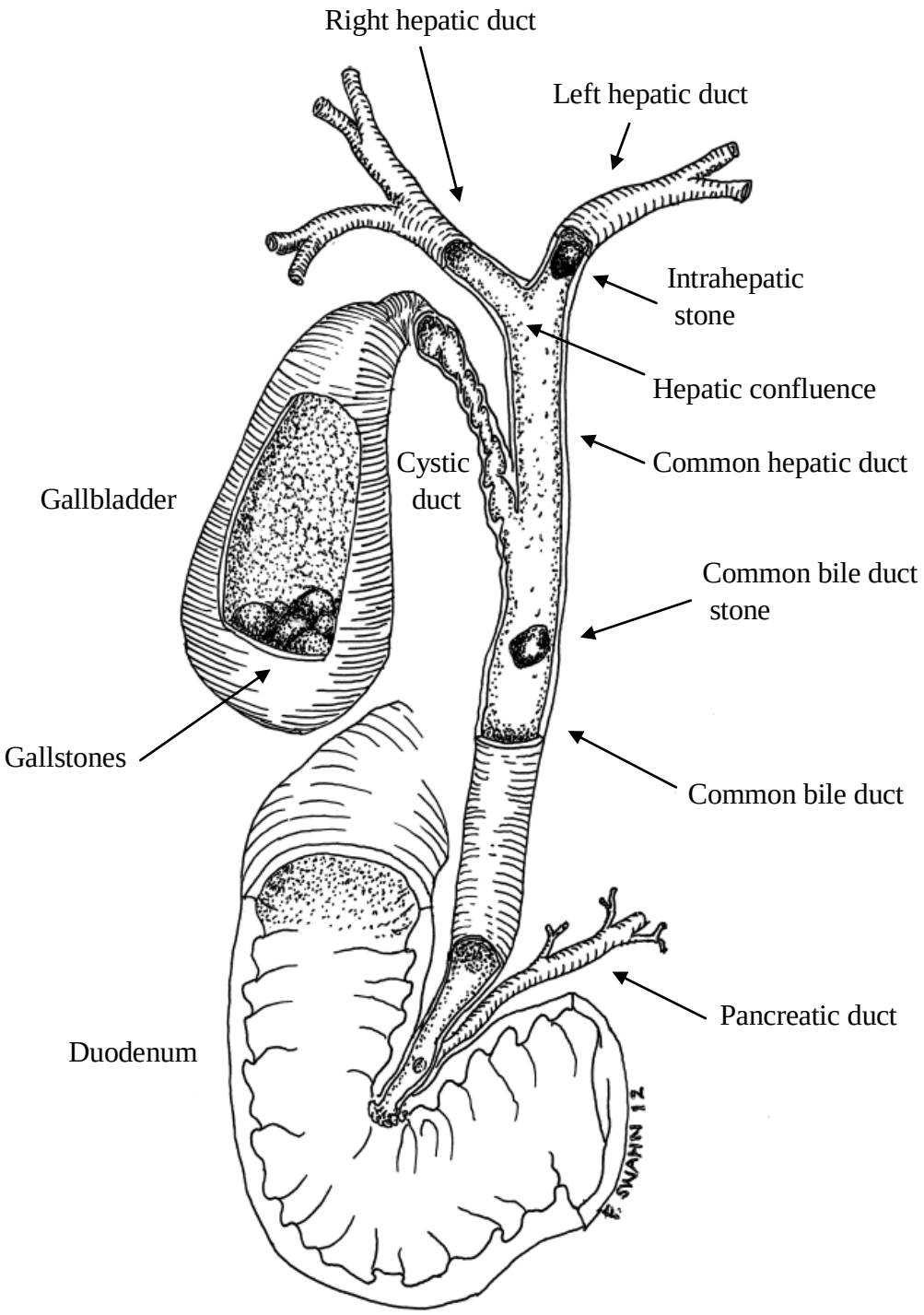


Figure 1. *Anatomy of the biliary system.* © Fredrik Swahn, 2012

2 BACKGROUND

2.1 GALLSTONE DISEASE

2.1.1 Historical perspective

Gallstone disease, caused by genetic predisposition, dietary habits and environmental conditions has occurred throughout human history. The earliest known gallstone dates back to ancient Egypt, discovered in the mummy of a priestess of Amen (1085-945 BC) and unfortunately destroyed during the bombing of London during World War II. The Greek physician Alexander Trallianus (525-605) was the first to describe "calculas" within the biliary ducts. With the revival of human dissection during the 15th and 16th century, gallstones ant their clinical consequences were described. In 1586, Marcellus Donatus of Mantua , Italy, published a thesis on biliary tract pathology with descriptions of stones expulsed from the gastrointestinal tract through vomits and stool. In 1676 Joenisius removed gallstones from a spontaneous biliary fistula thereby describing the first cholecystolithotomy.

The first steps of surgically addressing gallstones were taken by John S. Bobbs, Professor of Surgery at the Medical College of Indiana, USA. On June 15, 1867 he per-formed the first cholecystostomy in a patient operated for what he thought might be an ovarian cyst. He opened the gallbladder and removed around 50 gallstones. The patient had an uneventful recovery and a dramatic relief of pain.

Carl Langenbuch was credited to have performed the first surgical removal of the gallbladder, a cholecystectomy[5], in 1882. Believing that stones can reform and thus the bladder had to be removed, he adopted the technique that essentially has been the treatment of choice to this day.

During the following decades, steps were taken to improve diagnosis and treatment of gallstone related complications. The novel technique of radiology discovered by Wilhelm Conrad Röntgen (1845-1923) enabled radiological contrast-enhanced studies of the gallbladder. Cholangiography was first attempted via the gallbladder in 1921 but due to frequent bile leakage not clinically feasible until the development of the transhepatic route, in 1952. Intraoperative cholangiography (IOC) during cholecystectomy, a radiologic contrast-based examination of the bile duct was first described in 1937 by Mirizzi, to help delineate the anatomy of the biliary tree in case of advanced biliary disease[6].

During the second part of the 20th century, the cholecystectomy became a routine procedure performed in millions of patients all over the world. Even though methods for minimal invasive cholecystectomies were developed during the 1980s, such as mini-laparotomy, with a very small subcostal incision, few could predict the dramatic paradigm shift with the introduction of the laparoscopic cholecystectomy. Prior to 1990, the only field in medicine routinely using laparoscopy was gynaecology,

mostly for relatively short, simple procedures such as a diagnostic laparoscopy and tubal ligation.

Erich Mühe[7] is recognised for the first laparoscopic cholecystectomy in 1985. In the beginning, the new technique was met with disbelief and scepticism by fellow German surgeons. His procedure was described as “Mickey Mouse surgery” while others remarked “small brain - small incision.” It was not until the French surgeons Mouret, Dubois and Perissat in 1987-1988, after the introduction of video technology, that information about the new procedure successfully was spread to the wider surgical community. In 1989, Perissat presented his video of a laparoscopic cholecystectomy at the American Gastrointestinal Endoscopic Surgeons (SAGES) meeting in Louisville, KY, USA, and attracted great attention. A few months later Dubois's paper “Coelioscopic Cholecystectomy” was published in Annals of Surgery and found a large American audience[8]. Within a few years, the laparoscopic technique gained tremendous spreading but was initially restricted to uncomplicated gallstone disease. Acute cholecystitis and common bile duct stones were considered as contraindicated. Today, more than two decades later, laparoscopic cholecystectomy is used both in elective and emergent settings, addressing complicated gallstone disease making the open approach almost a rare event mainly used for particularly difficult cases.

2.1.2 Gallstone formation

Cholesterol stones are the most common group of gallstones (~90%) and form in the gallbladder[9]. They consists of cholesterol monohydrate and form due to supersaturated bile. Black stones (~2%) also form primarily in the gallbladder but are related to excessive levels of bilirubin in the bile. Brown pigment stones (~8%) form not only within the gallbladder but also within the intrahepatic and extrahepatic ducts[9]. They are infected with enteric bacteria or parasites and are usually associated with ascending cholangitis[9, 10]. Key mechanisms associated to the forming of gallstones are beside cholesterol or bilirubin supersaturation and infection also hypomotility of the gall-bladder[11] and disturbed enterohepatic circulation[12]. Genetic[13] (family history and ethnicity), environmental[14] (e.g. drugs and surgery) and lifestyle factors[15] (hyperchaloric diet, physical inactivity, obesity and rapid weight loss) have been identified as risk factors for gallstones.

2.1.3 Gallstone epidemiology

Gallstone disease prevalence is defined as patients with proved presence of gallstones and patients with evidence of cholecystectomy. The prevalence can be assessed by various techniques such as ultrasonography, cholecystography and autopsy surveys. The prevalence of gallstones in Europe and North America have been estimated to 10-20%[16, 17] of the population and is related to female gender and advanced age. In Sweden, Muhrbeck et.al. (1995) using a population-based screening of men and women

aged between 40 and 60 years, found that the overall prevalence was 15%. Women had a prevalence of 11% at the age of 40 and 25% at the age of 60. The corresponding percentages among men were 4% and 15%[18]. Once one or more gallstones are present, they may grow, shrink, or remain essentially the same size for years. The incidence or rate of gallstone formation has been estimated using ultrasonography. Patients free of gallstones at baseline examination were re-evaluated within a 5-year period and the incidence of gallstones was estimated to be 1.39 per 100 person-years[19].

2.1.4 Natural history of gallstones

Although evidently common, only a minority of patients with gallstones will become symptomatic. Most gallstones (60-80%)[20] do not generate symptoms and are incidentally found during radiology[21, 22]. Patients with asymptomatic gallstones are at a low risk of developing symptoms and studies have shown that approximately 1-2% of asymptomatic patients annually develop serious symptoms or complications[23]. However, a Swedish study concluded that nearly one out of ten patients with asymptomatic gallstones may be expected to develop symptoms or complications that require treatment within 5 years[24]. Why some stones remain silent without causing symptoms is still unclear and no differences in number, size or composition have been found comparing asymptomatic and symptomatic stones[25].

2.1.5 Complications of gallstone disease

2.1.5.1 Biliary colic

Biliary colic is the classic manifestation of gallstone disease defined as pain in the epigastrium and/or hypochondrium lasting more than 30 minutes[26]. It is caused by an obstruction of the gallbladder by a gallstone, at the neck or in the cystic duct. This obstruction results in increased pressure in the gallbladder and subsequent pain. However, the symptomatology of gallstones is often difficult to distinguish from other disorders with similar patterns regarding pain and associated symptoms, most commonly dyspepsia[27]. Studies have shown that comparing gallstone disease with dyspepsia, abdominal pain was generally related to gallstones, whether unspecified or localized in the upper abdomen[28]. Pain radiating to the back or right shoulder was more strongly associated with gallstones than unspecified upper abdominal pain. The character of the pain is often steady or comes in attacks lasting for longer than 30 minutes rather than pain in waves that suggests other conditions than gallstones[29]. Although a confirmed relationship between biliary colic and gallstones exists, the discriminative capacity is low. Biliary colic occurs in 20% of patients with gallstones and in 6% of patients without gallstones[30].

Biliary colic has been shown to have an association with unspecified food intolerance[28], however no specific provoking food item has been identified. It is

somewhat noteworthy that fat intolerance, with probably the most commonly suggested relationship to symptomatic gallstone disease, never have been significantly associated in study settings[30].

In conclusion, gallstone-associated symptoms are non-specific, and accurate diagnosis cannot rely on the clinical assessment alone. However, a careful clinical evaluation can guide patient selection for diagnostic imaging and facilitates the appropriate management of those found to harbour stones.

2.1.5.2 Acute cholecystitis

Acute cholecystitis is an acute inflammatory disease of the gallbladder. In 90-95% of cases, it is associated with gallstones[31-34], but many factors such as ischemia, infection by microorganisms, collagen disease and drugs may also contribute to acute cholecystitis. This inflammatory disease accounts for 3-10%[35, 36] of all patients with abdominal pain and develops in 1-3% of patients with symptomatic gall stones[23]. Most commonly, acute cholecystitis is caused by obstruction of the cystic duct by gallstones or by biliary sludge impacted at the neck of the gall bladder. If the obstruction is partial and of short duration, the patient experiences transient biliary colic. If the obstruction is complete and with long duration, the increased intraluminal pressure results in biliary stasis and triggers an acute inflammatory response[37].

The Tokyo Guidelines for the management of acute cholecystitis were developed in 2007 and suggested a global definition as well as severity grading of acute cholecystitis[38] (Table 1).

Table 1. *Tokyo Guidelines diagnostic criteria for acute cholecystitis.*

A. Local signs of inflammation:
(1) Murphy's sign, (2) Right upper quadrant mass/pain/tenderness
B. Systemic signs of inflammation:
(1) Fever, (2) elevated CRP, (3) elevated WBC count
C. Imaging findings:
Imaging findings characteristic of acute cholecystitis
Suspected diagnosis: One item in A + one item in B
Definite diagnosis: One item in A + one item in B + C

Acute hepatitis, other acute abdominal diseases, and chronic cholecystitis should be excluded

CRP C-reactive protein, *WBC* white blood cells

For acute cholecystitis, abdominal ultrasonography and computed tomography (CT) are the imaging studies most commonly used. Sonograms typically show pericholecystic fluid (fluid around the gallbladder), distended gallbladder, oedematous gallbladder wall

and gallstones. Ultrasonography has a high sensitivity (90-95%)[39] in detecting acute inflammation of the gallbladder and should be considered for initial evaluation due to safety and cost-effectiveness[40].

Acute cholecystitis is a very heterogeneous disease ranging from mild subclinical inflammation to necrotizing cholecystitis with perforation, biliary peritonitis and sepsis. In addition to diagnostic criteria, the Tokyo Guidelines group identified the need of a standardized severity grading system for the development of differentiated treatment algorithms and facilitation of comparable research findings[41] (Table 2).

Table 2. *Tokyo guidelines severity assessment criteria for acute cholecystitis.*

''Grade III'' (severe) acute cholecystitis is associated with dysfunction of any one of the following organs/systems	
1. Cardiovascular dysfunction	Hypotension requiring treatment with dopamine >5 μg/kg per min, or any dose of norepinephrine
2. Neurological dysfunction	Decreased level of consciousness
3. Respiratory dysfunction	PaO2/FiO2 ratio<300
4. Renal dysfunction	Oliguria, creatinine >2.0 mg/dl
5. Hepatic dysfunction	PT-INR>1.5
6. Haematological dysfunction	Platelet count<100,000/mm^3
''Grade II'' (moderate) acute cholecystitis is associated with any one of the following conditions	
1. Elevated WBC count (>18,000/mm^3)	
2. Palpable tender mass in the right upper abdominal quadrant	
3. Duration of complaints>72 h	
4. Marked local inflammation (gangrenous cholecystitis, pericholecystic abscess, hepatic abscess, biliary peritonitis, emphysematous cholecystitis	
''Grade I'' (mild) acute cholecystitis does not meet the criteria of ''Grade III'' or ''Grade II'' acute cholecystitis. Grade I can also be defined as acute cholecystitis in a healthy patient with no organ dysfunction and mild inflammatory changes in the gallbladder, making cholecystectomy a safe and low-risk operative procedure	

WBC white blood cell

Patients with severe acute cholecystitis may have mild jaundice caused by inflammation and oedema around the biliary tract causing a direct pressure on the biliary tract from the distended gall bladder. However, concentrations of bilirubin >60 μmol/l suggest a diagnosis of common bile duct stone or Mirrizzi's syndrome (obstruction by a stone impacted in the neck of the gallbladder compressing the common hepatic duct).

Early stage acute cholecystitis is generally considered to be non-bacterial but with increasing inflammation and ischemia of the gallbladder wall, overgrowth of enteric organisms and bacterial translocation may occur with subsequently increased morbidity and mortality[37, 42]. The role of antimicrobial therapy in early and non-severe cases of acute cholecystitis is unclear. In these patients, antimicrobial therapy is at best

prophylactic, preventing progression to infection. In other cases, with clinical findings of a systemic inflammatory response, antimicrobial therapy is therapeutic, and treatment may be required until the gallbladder is removed[43].

2.1.5.3 Chronic cholecystitis

Chronic cholecystitis is a disorder of the gallbladder with a thickened, shrunken bladder unable to properly concentrate, store, and release bile. The mucosa becomes atrophic and the normal bladder tissue is replaced by connective tissue in all wall layers. In long standing cases, the gallbladder wall may calcify, sometimes called a porcelain gall-bladder. The mechanisms leading to chronic cholecystitis are not settled but it is usually believed to be caused by repeated attacks of acute cholecystitis. There is no relationship between the severity of inflammation and number of gallstones and findings suggest that chronic inflammatory changes can occur in the gallbladder mucosa prior to the appearance of macroscopic stones[44] Chronic acalculous cholecystitis, inflammation with absent stones, have been reported in as much as 5% of cholecystectomy specimens[45].
Chronic cholecystitis is known to predispose for difficult surgery with increased conversion rates at laparoscopic cholecystectomy[46] and is considered to be a risk factor for gallbladder carcinogenesis[47, 48].

2.1.5.4 Common bile duct stones

Common bile duct stones (CBDS) typically originate in the gallbladder and migrate. This is called secondary stones and should be differentiated from primary CBDS, a relative rare condition, with stones developing in the bile ducts mainly due to stasis and biliary infection.
The prevalence of CBDS in patients with symptomatic gallstones is 10-20%[49-54]. The percentage of patients with CBDS detected at 2989 cholecystectomies in a Swedish study was 10.2%[55]. Another Swedish study of 647 cholecystectomies where 88% had IOC, 8% of the patients were found to have CBDS, and the majority (53%) were discovered during IOC and thus not preoperatively detected[56].

Transabdominal ultrasound, excellent for the detection of gallbladder stones, is not as sensitive in the detection of CBDS. However, together with clinical suspicion it still is considered a first line modality due to its simplicity and safety, and can be used in selecting patients to more sensitive evaluations by computed tomography (CT) or magnetic resonance cholangiopancreatography (MRCP). Peroperative IOC is the optimal method for CBDS detection during cholecystectomy but is nevertheless controversial. Although safe and easy to perform, IOC adds time and costs to the procedure. It is furthermore evident that a fairly high percentage of CBDS will pass spontaneously. In a prospective study by Collins et. al., one third of cholecystectomised patients with suspected CBDS on peroperative IOC were found to have spontaneous ductal clearance within 6 weeks postoperatively[57]. On the other hand, it has been suggested that patients referred with post cholecystectomy complications due to residual CBDS are more frequent than generally considered[58] and the topic of how to optimally detect and handle peroperative CBDS remains unsettled.

Although the natural history of CBDS is significantly less known than that of gallbladder stones, it is evident that when ductal stones become symptomatic the consequences are often serious and can include pain, partial or complete biliary obstruction, cholangitis, or pancreatitis. It is recommended that patients with symptomatic CBDS have the stones removed, but the methods are still controversial. Stones can be removed preoperatively, by endoscopic retrograde cholangiopancreatography (ERCP), intraoperatively by surgical or endoscopic means or postoperatively by ERCP.

2.1.5.5 Biliary pancreatitis

CBDS may be trapped in the common bile duct in the ampulla above the sphincter of Oddi and cause biliary pancreatitis. It is believed that 30%-60%[59] of acute pancreatitis cases are due to obstructing gallstones, with small, numerous stones and a large cystic duct being considered risk factors[60]. The majority of obstructing stones will be cleared spontaneously within 48 hours making early intervention with ERCP and sphincterotomy useless in terms of limiting the severity of the pancreatitis[61]. However, as the risk of recurrent episodes of acute pancreatitis is as high, patients with an episode of biliary pancreatitis should be considered for preventive cholecystectomy[62].

2.1.5.6 Gallbladder cancer

Gallbladder cancer is a rare malignancy with considerable geographical variations. It affects 1.2 per 100 000 persons in USA annually but varies considerable worldwide. In contrast, gallbladder cancer is considered a common form of cancer in Delhi, India, with 21.7 cases per 100 000 persons[63]. The prognosis is generally considered to be poor[64]. Gallstones have been stipulated as a risk factor for gallbladder cancer, with special emphasis to large stones and the time stones have been present in the bladder[65]. Recently, the causal relationship between gallstones and gallbladder cancer have been questioned and it is possible that the excretion of cholesterol from the liver, causing cholesterol stones, is joined by the hepatic excretion of other toxic compounds which in turn may be carcinogenic[66].

Patients with gallbladder wall calcification, i.e. porcelain gallbladder, have been associated with increased risk of developing gallbladder carcinoma. A systematic review of 124 calcified bladders showed a 6% rate of gallbladder cancer suggesting that prophylactic cholecystectomy for incidental radiological findings of this condition is suitable[67].

Gallbladder polyps are considered to be a risk factor of gallbladder cancer with increasing rate of malignancy with increasing size of the polyp. However, the risk of malignancy resulting from incidentally detected small polyps is extremely low and watchful waiting can safely be recommended for polyps less than 10 mm[68]. Gallbladder cancer more commonly arises from dysplastic, rather than adenomous,

lesions, which suggests that identification of a thickened gallbladder wall should render more consideration than what is practice today[65].

2.1.6 Treatment of gallstone disease

2.1.6.1 Asymptomatic gallstones

Asymptomatic gallstones, encountered incidentally without symptoms, have become an increasing problem as imaging procedures such as trans-abdominal ultrasound are readily available, safe and relatively inexpensive. It is particularly troublesome if functional disorders, with symptomatology resembling gallstone disease are incorrectly seen as a consequence of encountered stones. The crucial question is that if prophylactic cholecystectomy is justified regarding prevention of complications contra operative risk. In one study, a biliary complication was observed in less than 3% of asymptomatic gallstones after 10 year of follow-up[69]. Another study, following asymptomatic patients for 24 years, reported a 6% cholecystectomy frequency due to the development of symptoms[70].

There have been no randomized controlled trials comparing cholecystectomy versus no cholecystectomy in patients with asymptomatic gallstones[71]. However, given the substantial knowledge regarding the commonness of gallstones, low risk of developing complications and cholecystectomy related morbidity, cholecystectomy cannot be recommended for patients having asymptomatic gallstones[72]. This recommendation includes patients with incidental findings of gallstones during surgery for other conditions[73].

2.1.6.2 Biliary colic

Laparoscopic cholecystectomy is considered the preferred treatment for symptomatic gallstone disease, but the evidence for this could be questioned. Symptoms vary greatly and retrospective studies, following patients with symptomatic gallstones over several years suggest that cholecystectomy is not suitable for all patients and expectant management may also be a valid therapeutic approach[69, 74]. A Norwegian randomized controlled trial on patients with symptomatic, uncomplicated gallstone disease, compared outcome after surgery or observation. No important differences in outcome between the groups were seen at 5 or 14 years of follow-up[75, 76].
In conclusion, surgery is still the preferred treatment among patients with intolerably frequent episodes of biliary colic but watchful waiting should likewise be an option considering mild symptoms, especially among elderly.

2.1.6.3 Acute cholecystitis

The therapeutic standard for acute cholecystitis is cholecystectomy[32], even though the heterogeneity of this group necessitates alternative treatments.
Between 10-15% of all cholecystectomies are performed due to acute cholecystitis[77]. Today, laparoscopic cholecystectomy is the preferred treatment as it involves shorter hospital stay and has similar frequency of morbidity and mortality as open cholecystectomy[78-81].

The appropriate timing of cholecystectomy in patients with acute cholecystitis has been debated and addressed in several randomized controlled trials[82-85]. The results suggest that conversion rates and overall complications following surgery within the first week of symptoms are similar to interval operation, after 6-8 weeks, but surgery within the first week leads to significantly shorter hospital stays[86, 87]. Furthermore, there is some evidence supporting immediate cholecystectomy, preferably with surgery as soon as possible following symptom onset (if at all possible within 72 hours of symptom onset)[88-90]. In the only large, registry based, study of 4113 patients with acute cholecystitis, complications associated to cholecystectomy timing were studied. Cholecystectomy at admission day had lower conversion rates, less complications, lower reoperation rates as well as shorter postoperative hospital stay compared to operation 6 days after admission[91].

No randomized controlled trials have addressed the optimal surgical treatment for acute cholecystitis with regards to grade of severity. The Tokyo Guidelines proposed an algorithm recommending early laparoscopic cholecystectomy for mild forms (grade I), early laparoscopic or open cholecystectomy within 72 hours for moderate (grade II) and urgent management of organ dysfunction, control of local inflammation by drainage and/or cholecystectomy for severe forms (grade III)[92]. As cholecystectomy can be associated with substantial morbidity and mortality within subgroups of patients[93, 94], cholecystostomy, percutaneous drainage of the gallbladder, may be an alternative treatment for high risk patients but this should be further evaluated in a randomized study setting[95].

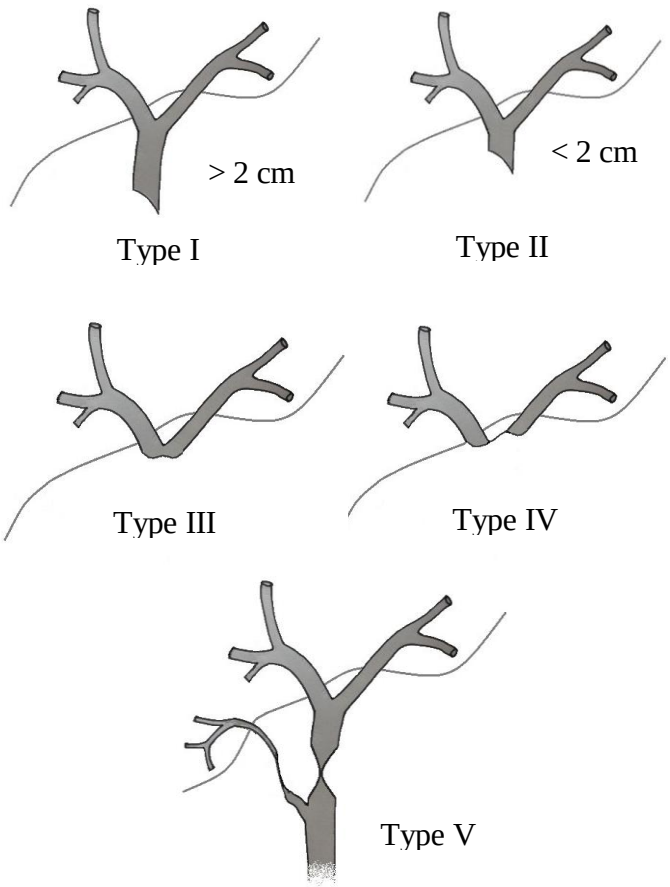
2.2 IATROGENIC BILE DUCT INJURY

Iatrogenic BDI during cholecystectomy is one of the most dreaded complication among surgeons performing cholecystectomy. This thesis addresses important questions concerning occurrence, consequences and prevention of such injuries.

2.2.1 Classification of bile duct injury

The management and outcome of BDI vary considerably and are highly dependent on injury localization, extent of the lesion and possible associated injuries such as vascular or bowel injuries. An optimal classification system has to be detailed enough to differentiate between injuries with different clinical and therapeutic entities, but simple enough to be adopted and used. Regarding BDI, no single classification system has been globally accepted as standard, making the comparison of research findings troublesome and precluding efficient metanalyses.

2.2.1.1 Bismuth's classification



Traditionally, BDI have been classified according to Bismuth's classification[96], originating from the era of open surgery and intended to help surgeons to choose the most suitable repair technique for postoperative biliary strictures. It describes the most distal level at which healthy biliary mucosa is available for anastomosis. The introduction of laparoscopic cholecystectomy led to new and more severe injuries, not possible to classify using Bismuth's system[97]. However, it still remains as an important baseline for newer and more differentiated classification systems.

Figure 2. *Bismuth classification of BDI.*

2.2.1.2 Strasberg's classification

The Strasberg classification[97] (Figure 3) was introduced in 1995, when the laparoscopic technique was well established. It extended Bismuths' classification to a more comprehensive categorisation, with the ability to describe and differentiate more types of extrahepatic injuries. Strasberg's classification is the most commonly used among clinicians, stratifying injuries from type A to E, with E-injuries further subdivided according to Bismuth's classification. One limitation with Strasberg's classification is that it does not include concomitant vascular injuries, which is highly relevant due to the added complexity and morbidity associated with such lesions[98].

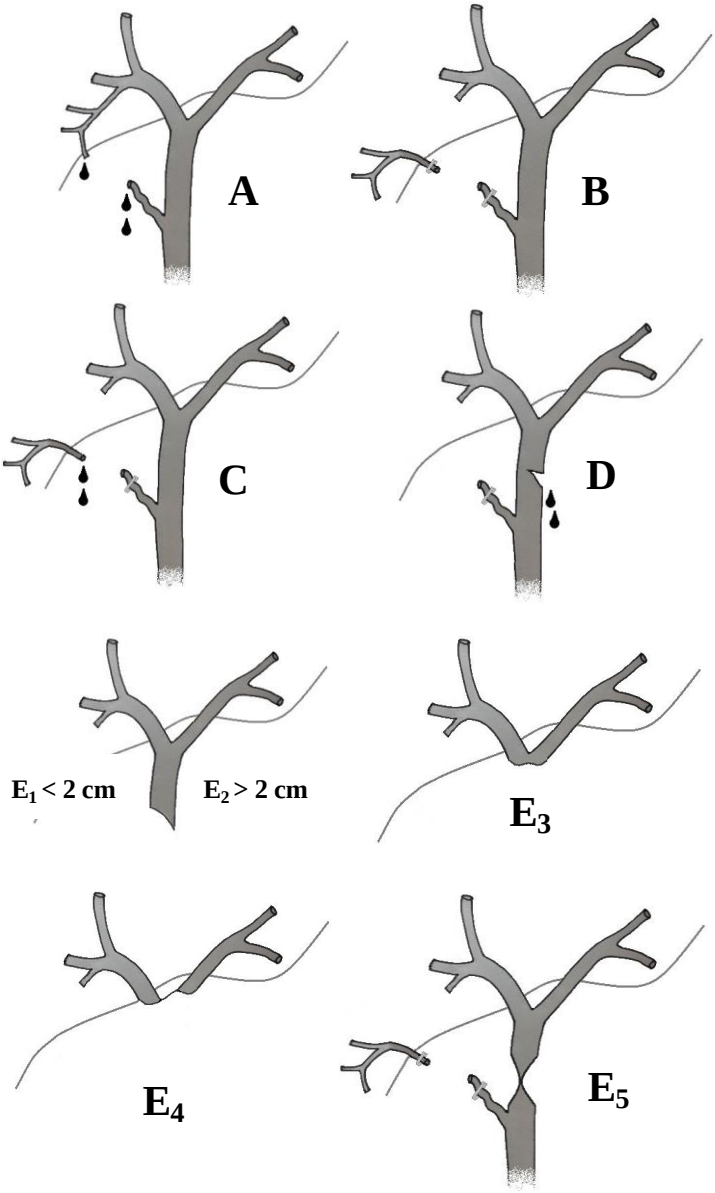
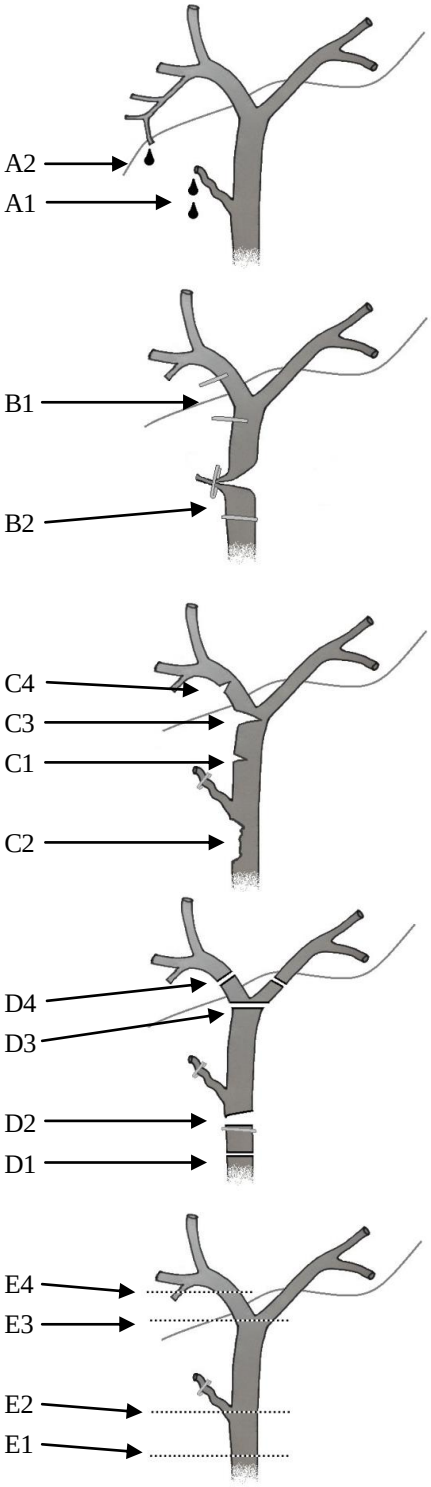


Figure 3. *Strasberg classification of BDI.*

2.2.1.3 Hannover classification

The Hannover classification[99] of BDI was introduced in 2007, offering a strong association between injury discrimination and treatment and including vascular injury (Figure 4). Although probably too complex to become commonly used in the daily clinical setting, it offers advantages in research, and the detailed injury description is fully transferable to the majority of other existing classification systems. Concomitant vascular injury is denoted with a suffix; right hep. artery (d), left hep. artery (s), proper hep. artery (p) common hep. artery (com), cystic artery (c), portal vein (pv) (e.g. D3d).



Type A
Peripheral bile leak (with reconnection to the main bile duct system)
- A1 Cystic duct leak
- A2 Leak in the region of the gallbladder bed

Type B
Stenosis of the main bile duct without injury (i.e. caused by a clip)
- B1 Incomplete
- B2 Complete

Type C
Tangential injury of the common bile duct
- C1 Small punctiform lesion (< 5 mm)
- C2 Extensive lesion (> 5 mm) below the hepatic bifurcation
- C3 Extensive lesion at the level of the hepatic bifurcation
- C4 Extensive lesion above the hepatic bifurcation

Type D
Completely transected bile duct
- D1 Without defect below the hepatic bifurcation
- D2 With defect below the hepatic bifurcation
- D3 At hepatic bifurcation level (with or without defect)
- D4 Above the hepatic bifurcation (with or without defect)

Type E
Strictures of the main bile duct
- E1 Main bile duct short circular (< 5 mm)
- E2 Main bile duct longitudinal (> 5 mm)
- E3 Hepatic bifurcation
- E4 Right main bile duct/segmental bile duct

Figure 4. *Hannover classification of BDI.*

2.2.1.4 Other classification systems

As a complement to the original Bismuth's classification, other types of classification systems for BDI have been proposed and are used to various extents. McMahon et. al.[100] suggested a division into major BDI (laceration > 25% of the bile duct diameter, transection of the common bile duct (CBD) or common hepatic duct (CHD) or post-operative bile-duct strictures) or minor BDI (laceration of CBD < 25% of diameter or laceration of cystic-CBD junction). The Amsterdam classification[101] subdivides into four groups with relation to suggested treatment options. Stewart-Way's[102] and Csendes'[103] classifications addresses the injury mechanism, whereas the Neuhaus'[104], Siewert[105] and Chinese University of Hong Kong[106] describes possible lesions in slightly different ways.

2.2.2 Incidence of bile duct injury

Numerous authors have reported incidence figures of BDI before and after the introduction of the laparoscopic technique. During the open era the incidence of BDI was reported on an average of 0.25% (ranging from 0% to 0.90%)[107-113] and increased to 0.55% (ranging from 0.15% to 0.74%)[114-122] after the introduction of laparoscopy. The increased incidence of BDI observed during the 1990s can to some extent be explained by the learning curve of the laparoscopic technique[120], but it seems like the incidence figures remains moderately elevated throughout the laparoscopic period.

Some concerns can be raised regarding the comparability of these BDI-incidence reports. In the period of open cholecystectomy, BDI incidence figures constitutes mainly of single centre (or a few multi-centre) case series or questionnaire surveys with self-reported data and possible doubts regarding BDI identification and definition. After the introduction of laparoscopy, larger population based studies were conducted with more objective complication identification although to the majority only measuring major BDI requiring surgical repair. "True" incidence figures of the whole range of BDI can probably only be achieved by large prospectively collected quality registries, with sufficient coverage and objective registration of peroperative and postoperative complications. Although national registries of gallstone-related interventions now exist, no data of sufficient quality have yet been reported.

2.2.3 Consequences of bile duct injury

2.2.3.1 Morbidity and mortality

A BDI is associated with substantial morbidity. The expected short hospital stay or planned day-care surgery of an uncomplicated cholecystectomy is in sharp contrast to the often complicated, prolonged and uncertain recovery after a BDI.

The majority of BDI are not detected during the initial cholecystectomy[115, 123, 124] and the diagnosis is preceded by symptoms and complications due to bile leakage or stricture formation. Undiagnosed or improperly handled post-operative bile leakages have high risk of subsequent generalized peritonitis. Biliary peritonitis has been shown to be an independent risk factor for death in comparison to other causes of secondary peritonitis, emphasizing the need of early diagnose and intervention in this group of patients[125]. Percutaneous, endoscopic or surgical interventions and re-interventions add complexity and further risks, making the patients often committed to a decade of post-operative follow-up[123].

In 2003, a nationwide population-based study of 1 562 450 cholecystectomies with 7911 surgically reconstructed BDI within the Medicare social insurance program in USA, Flum et. al.[2] reported devastating outcome after reconstructed BDI. Only 19.2% of BDI patients survived to the last common follow 9.2 years after the operation compared to 55.2% in the non-injured group. The adjusted hazard ratio (HR) for death among BDI-patients was 2.8 times higher than that of non-injured patients. These finding were in sharp contrast to the relative good long-term results previously reported from the open and laparoscopic periods, which showed mortality rates ranging from 0-14.2% based on a total of 602 BDI patients during an average follow-up period of 41.3 months[103, 126-139]. In 2007, DeReuver et. al.[140] published a single centre study of 500 BDI patients in a Dutch national referral hospital during 1990-2005. They reported excellent long term result and mortality rates not significantly different from the general population. In comparison, the results from Flum's study are potentially seriously confounded, as the study population from Medicare beneficiaries consisted mainly of elderly and persons with substantial healthcare needs and precarious economic situations, and only injured patients requiring surgical reconstruction were defined as BDI. Their results should thus be interpreted with care and are hardly representative to the general population. On the other hand, the contrasting figures of DeReuver et. al. could to some extent be explained by a selection of merely referred BDI, excluding patients that had already died due to complications prior to referral. However, the result undoubtedly reflects the importance of a multidisciplinary approach to BDI at an expertise hepatobiliary centre.

The morbidity and mortality risks associated with BDI are serious, but to fully comprehend the impact on afflicted patients, further studies with more carefully adopted selection criteria, are needed.

2.2.3.2 Quality of life

In one of the first studies addressing quality of life, Boerma et.al.[4] assessed the impact of BDI on physical and mental quality of life (QOL) using the standardized questionnaire SF-36. Despite excellent functional outcome after repair, 106 patients sustaining BDI reported reduced QOL compared to non-injured controls. De Reuver et. al.[141] reported a longitudinal QOL study of 403 patients that suffered BDI. They compared QOL after, on average 5.5 and 11 years following the BDI. Their results suggested that QOL was impaired compared to non-injured and no improvement during the follow-up period was observed. Further studies have confirmed these findings[142],

mainly regarding psychological factors, associating a worse outcome with prolonged treatment period and legal procedures. Patients suffering BDI are often disappointed and feel neglected by many surgeons' reluctance to admit their own mistakes, emphasizing the need of an honest doctor-patient communication and thorough information following BDI events.

2.2.3.3 Economic aspects

Surgery with complications goes with a need of substantial resources. An operation that leads to BDI adds not only hospital days, diagnostic radiology, expensive endoscopic or surgical interventions but also the costs of prolonged sick-leave and loss of production. A few studies have been conducted to estimate the economic impact of BDI. Andersson et. al.[143] calculated the annual costs per 1 000 000 inhabitants in Sweden by analysing actual in-hospital costs and loss of production of minor and major BDI. The average cost per patient was €21 837 for minor BDI and €107 568 for major BDI. After adjusting the figures by BDI incidence, the costs were estimated to be within the range of €136 787-€159 585 for minor BDI and €473 690-€608 789 for major BDI per million inhabitants.

In an American study, Savader et. al.[144] showed that for 49 BDI patients at the Johns Hopkins Hospital, Baltimore, Maryland, the average in-hospital costs associated with the complete treatment of the patients was $51 411 (€66 976), excluding the costs for sick-leave and loss of production.

From the medico-legal point of view, financial compensation is a measurement of the estimated economic burden associated with BDI. Statistically, surgeons are more at risk of litigation following laparoscopic cholecystectomy than they are after any other general surgical procedure, although with great differences between countries. In the UK, Roy et.al.[145] evaluated 83 claims following BDI during laparoscopic cholecystectomy between the years 2000 and 2005. An average of €64 681 were rewarded the patients and delayed recognition of the injury was correlated to increased risk of litigation. In comparison, the average payment per BDI claim was €12 795 in the Netherlands[146] and €650 000 in United States[147].

2.2.4 Prevention of bile duct injury

By far the best way to treat BDI is by prevention. But is this possible? Should a BDI be regarded as an unfortunate complication or is it a preventable error? In a Canadian survey, the majority of questioned surgeons felt that BDI could not be anticipated and as such is an inherent risk of the procedure[148]. On the other hand, many surgeons have reported large series of laparoscopic cholecystectomies without a single BDI[149]. To properly address this question, it is essential to understand the underlying mechanism of how BDI occur, most commonly by a misidentification or misinterpretation of biliary anatomy. Way et. al.[150] analysed 252 laparoscopic cholecystectomies with major bile duct injuries and came to the conclusion that in the

vast majority of BDI, the CBD or CHD were misidentified for the cystic duct or the surgeon dissected too close to the CHD. It was not faulty decision-making, lack of knowledge or plain clumsiness that caused the injury. Way et. al. concludes that when surgeons inspect the gallbladder, the subconscious brain seeks a recognizable pattern to match the mental model of the biliary tree. The brain makes a subconscious identification of the cystic duct (an illusive decision in the case of a BDI) and it is extremely difficult to change this perception. In laparoscopy, the perception is mainly visual in contrast to open surgery, in which haptic feedback can guide the surgeon to a correct interpretation of underlying structures. This difference in perception may to some extent explain the increased BDI incidence with laparoscopic approach.

To prevent BDI we thus have to find strategies aiding surgeons to make correct interpretations of the biliary anatomy; Risk factor identification makes the surgeon aware of patients or situations where the risk of misinterpretation is increased. Development of surgical techniques that emphasizes on making the few risky parts of a cholecystectomy more standardized and safe as well as the proper use of technology, e.g. IOC used in order to verify the anatomy.

2.2.4.1 Risk factors for bile duct injury

2.2.4.1.1 Advanced age

Advanced age has been proposed as a risk factor for BDI[118, 120, 122]. Physiologic tissue changes with ageing may be a possible explanation to some of the increased risk. However, even though these studies controlled for confounding factors, it is likely that they suffer from residual confounding. Older persons more commonly have higher comorbidity, and are thus more likely to have had complications such as acute and chronic inflammation and more frequently have adhesions obscuring the surgical field.

2.2.4.1.2 Gender

Male gender has been associated with difficult surgery during many abdominal procedures[151]. Although Grönroos et.al. showed evidence of the opposite[152], the few population based studies with sufficient power associates male gender to increased risk of BDI[118, 122, 153], although with questionable confounder adjustment. However, the mechanism of such association is not fully understood. It is possible that the male abdomen is more difficult when it comes to laparoscopic surgery, as significant higher conversion rates have been reported among men[154]. Furthermore, male gender has been associated with a higher rate of acute cholecystitis or sequele from previous acute cholecystitis[155] which increases the surgical difficulties. Another explanation might be that the proportion and distribution of obscuring intra-abdominal fat differs between genders.

2.2.4.1.3 Inflammation

As acute cholecystitis is associated with increased conversion rates and overall complications compared to uncomplicated gallstone disease, it has been almost generally accepted as a risk factor for BDI. However, the evidence for an association between acute cholecystitis and BDI is weak. Considering larger population-based studies addressing risk factors for BDI, no difference in BDI rates was observed

between patients with and without inflammation[118, 120, 156]. However, methodological limitations makes the results less powerful. Giger et. al.[153] suggested that acute cholecystitis should not be regarded as a risk factor when comparing to a heterogeneous control group consisting of patients with symptomatic gallstone disease *or* chronic cholecystitis. The only studies with reported significant increased BDI rates associated with acute cholecystitis are relative small case series[157, 158] from single institutions with the most dramatic impact of acute cholecystitis seen during the first years of the laparoscopic technique[158].

There are a number of issues related to the identification of associations between inflammatory changes of the gallbladder and BDI. The presence of acute cholecystitis in population based research is mainly based upon ICD-diagnosis codes, which have been proven unpredictable in many research settings[159]. In studies with acute or chronic cholecystitis defined by the surgeon's evaluation of the gallbladder during operation, the results are at high risk of being biased by the likely possibility of more severe descriptions by surgeons causing BDI. The possible relationship between inflammatory changes of the gallbladder and BDI has not yet been validly shown, and remains an important question as acute cholecystitis is a common and important indication for cholecystectomy.

2.2.4.1.4 Surgeon related risk factors for bile duct injury

The experience and characteristics of surgeons causing BDI have been addressed by many researchers. During the period of open cholecystectomy Andrén-Sandberg[160] noticed that the majority of surgeons causing the BDI were doing their residency. In 1995, Moore et. al.[161] reported that 90% of BDI occurred within the first 30 operations performed by an individual surgeon. Similarly, Gigot et. al.[138] reported a twofold incidence of BDI among surgeons with less than 50 cholecystectomies compared to surgeons with experience of more than 50 operations. In their analysis of Medicare beneficiaries, Flum et. al.[162] showed that BDI occurred mainly during a surgeons first 20 cholecystectomies. In addition, a survival analysis on the same cohort of patients showed slightly decreased mortality after BDI if the surgeon performing the cholecystectomy was a surgical specialist[2]. Furthermore, teaching hospitals have been related to a twofold increased risk of BDI in one study[118] whereas no difference was seen in another[163]. However, a proper and dedicated laparoscopic training program has the potential of reducing this increased BDI incidence among inexperienced surgeons[164].

The association between BDI and inexperience was most noticeable in the early years of the laparoscopic technique and has diminished since laparoscopic cholecystectomy became standard of care. It is furthermore obvious that experience is not a guarantee against BDI, as many injuries are caused by surgeons with more than 100 laparoscopic cholecystectomies[138].

2.2.4.1.5 Anatomical variations

Biliary tree anomalies have been reported to occur in 19-25% of patients[165, 166], and constitutes a risk factor for BDI. Most commonly, a right hepatic segmental or sub-segmental duct drains separately into the CHD between the hepatic confluence and the cystic duct or directly into the cystic duct. These anomalies increase the possibility of

misidentifying the aberrant duct as the cystic duct. If IOC is performed through an aberrant right segment or sub-segment duct, very few surgeons would recognize the "missing" segmental duct on the cholangiogram. It is thus the use of safe surgical technique that is most important in the prevention of BDI in cases of anatomical variations.

2.2.4.2 Safe surgical technique

As the main cause of BDI is due to misidentification of the CBD/CHD being the cystic duct, the goal of dissection is a conclusive identification of the cystic duct. A few strategies have been proposed for this: (1) Dissection of the main bile ducts so that the uniting point of the CBD and cystic duct is identified; (2) The infundibular technique. (3); The critical view of safety technique and (4) Intraoperative cholangiography.

(1) Laparoscopic dissection of the main bile ducts in order to identify the junction of the CBD and the cystic duct has been a method for reliable identification of the cystic duct prior to division. However, this method should not be encouraged as it is potentially very dangerous and the risk of damage to the CHD/CBD during dissection is increased.

(2) In the infundibular technique, the cystic duct is isolated and followed into the gallbladder by dissecting the front and back of the triangle of Calot. When the cystic duct gradually becomes the gallbladder infundibulum, it is taken as evidence of identification and the structure may be divided. Although the infundibular technique have been commonly used and taught, it has disadvantages. The cystic duct may be hidden, especially in cases of inflammation and suboptimal lateral traction of Hartmann's pouch. This may lead to a false infundibulum with subsequent misinterpretation of the CBD as the cystic duct[167].

(3) The critical view of safety technique, described by Strasberg in 1995[97] deals with the potential problems of the infundibular technique. The method requires complete dissection of the triangle of Calot and separation of the base of the gallbladder from the liver bed prior to division of the suspected cystic duct. After proper dissection, only two structures enter the gallbladder, the cystic duct and the cystic artery, which can be divided safely. The critical view of safety should be considered as golden standard technique of laparoscopic cholecystectomy with a likely reduction of misidentification injuries if properly used.

(4) With the introduction of laparoscopic cholecystectomy and the subsequent increase in BDI, IOC, formerly used mainly for CBDS detection, was introduced as a "road-map" in order to avoid major BDI. Today, more than two decades since the laparoscopic procedure was introduced, the use of IOC to prevent BDI is probably one of the most debated and controversial topics in this field of surgery. It thus deserves a thorough analysis.

2.2.4.3 Intraoperative cholangiography

A search of intraoperative cholangiography and cholecystectomy in the online bibliographic database PubMed renders 1420 results, of which 260 have been published during the last 20 years. Despite the immense research on this topic, the level of scientific evidence is generally poor and the key questions of whether IOC prevents BDI and if it should be routinely or selectively used, are being far from settled.

Surgeons who do not use IOC, claims it to be unnecessary, costly and time consuming and that BDI can be avoided without using IOC. Selective users believe they can identify the subgroup of patients at high risk of BDI and apply IOC selectively on them. Furthermore, selective IOC users consider the patient's benefit, from the detection of unexpected common bile duct stones by IOC, to be limited not justifying the added costs. Routine users argue that it is not possible to identify patients with no risk of BDI and thus routine use is safer.

The main problem in studies of a hypothesized causal association between IOC and reduced BDI rates is due to the relative uncommonness of BDI. Given an expected reduction in BDI rate from 0.4% to 0.2% with the use of IOC, such a trial would require a sample size of more than 10 000 patients to detect a difference with 80% power. Nevertheless, at least four randomized controlled trials (RCT) of IOC vs. no IOC and one of routine vs. selective IOC have been conducted[168-173]. The mean sample size of these studies was 233 (115-303), a total of 4 BDI was observed and the results were inconclusive (Table 3). Unfortunately, the heterogeneity of these studies precludes further meta-analyses[174].

Table 3. *Randomized controlled trials of IOC and the risk of BDI.*

				BDI		
Author	**Year**	**Included patients**	**No. of patients**	**IOC**	**No IOC**	**p-value**
Khan et. al.	2011	Low risk of CBDS, LC	190	0	1	NS
Nies et. al.	1997	Low risk of CBDS, LC, OC	275	0	1	NS
Soper et. al.	1994	Low risk of CBDS, LC	115	0	0	NS
Hauer-Jensen et. al.	1986,1993	Low risk of CBDS, OC	280	0	0	NS
				Selective IOC	**Routine IOC**	
Amott et. al.	2005	Non-selective, LC	303	1	1	NS

LC: Laparoscopic cholecystectomy, OC: Open Cholecystectomy, NS: Non significant

Addressing the same question of an IOC-BDI association, and suffering identical sample-size issues, many researchers have reported their experiences with case series at single centres[175-179]. Due to the sample-size problem, none of these series offers valid evidence on the association between IOC and BDI.

In an effort to handle the problem of small sample-sizes, Ludwig et. al.[180] performed a meta-analysis of 26 different single-centre case series, identifying 405 major injuries and performed a sub-group analysis on 103 BDI patients and the relationship to IOC. With routine IOC usage, 90% of injuries could be diagnosed intraoperative, compared to a 45% intraoperative detection rate in the selective IOC group. Furthermore, small incomplete incisional injuries to the CBD were the most common injury in the routine group whereas larger dissection injuries > 5 mm were most common in the selective group. The results speak in favour of routine IOC use and hypothesis a down-staging effect of IOC on BDI severity. However, major methodological questions regarding selection, heterogeneity and possible confounders makes these general conclusions questionable.

Nuzzo et. al.[181] collected questionnaire-based information of 56 591 cholecystectomies from 184 Italian hospitals, and they found no significant benefit comparing routine vs. selective use of IOC. However, the categorization and definition of routine or selective use is questionable, and self-reported data, especially concerning surgical errors, should be interpreted with care.

Population-based studies on administrative data have the advantage of large sample sizes, which makes it possible to test for associations between outcome (BDI) and exposure (IOC). Possible confounder adjustment, inherently addressed by randomization in an RCT, can be dealt with using logistic regression modelling. Larger population based studies, reporting on the IOC-BDI relationship, are listed in table 4.

In the first large population based study by Fletcher et.al.[118], 20 084 cholecystectomies in Western Australia were searched for complications including BDI. A reduction of intraoperative complications, "bile duct injuries, other injuries and major bile leaks", were seen with the use of IOC (Odds ratio (OR) 0.5 95% CI 0.35-0.70). In 2006, Hobbs et. al.[182] using the same data together with cholecystectomies from the subsequent four years, and a total of 33 309 operations, reported reduced complication rates with an OR of 0.72 (95% CI 0.55-0.93). In two studies, using 30 630 and 1 570 361 cholecystectomies respectively, Flum et. al.[162, 183] analysed reconstructed BDI and noticed a multiadjusted significant OR for BDI of 0.63 and 0.58, respectively, when IOC was used compared to when it was not used. Using identical methodology, Waage et. al.[122] analysed 152 776 cholecystectomies in the Swedish Inpatient Registry between 1987 and 2001, and noticed an adjusted OR of 0.75 (95% CI 0.59-0.92) for reconstructed BDI when IOC was used.

In contrast to these findings Z'Graggen et.al.[184] in 1998 and Giger et.al.[153] in 2011 used the Swiss Association of Laparoscopic and Thoracoscopic Surgery, (SALTS), registry to evaluate complications during cholecystectomy. No significant effect of IOC was seen on, somewhat poorly defined, BDI.

Table 4. *Population based studies of the association between IOC and BDI.*

Author	Design	Study base	No. of patients	Period	BDI definition	No. Of BDI	Frequency of IOC	Effect of IOC
Giger et. al. 2011	Cohort study	LC, SALTS registry	31 838	1995-2005	Not stated	101	37%	NS
Waage et. al. 2006	Cohort study	LC + OC, Swedish Inpatient Registry	152 776	1987-2001	Reconstructed BDI (ICD)	613	62%	Adj OR 0.75 (0.59-0.92)
Hobbs et. al. 2006	Cohort study	LC + OC, Western Australian Data Linkage System	33 309	1988-1998	All BDI (ICD screening > record review)	78 (+182 bile leaks)	41%	Adj OR 0.72 (0.55-0.93)
Nuzzo et. al. 2005	Multicentre survey	Questionnaire to surgeons at 184 of 316 Italian hospitals	56 591	1998-2000	Not stated	235	Not stated	NS comparing routine vs. selective
Flum et. al. 2003	Cohort study	LC + OC, Medicare beneficiaries	1 570 361	1992-1999	Reconstructed BDI (ICD)	7911	39%	Adj OR 0.58 (0.55-0.62)
Ludwig et. al. 2002	Review	Single and multicentre studies (not specified)	327 523	Not stated	Major BDI	Not stated	Not stated	No OR
Flum et. al. 2001	Cohort study	LC in Washington State hospital discharge database	30 630	1991-1998	Reconstructed BDI (ICD)	76	64%	Adj OR 0.63 (0.40-0.90)
Fletcher et. al. 1999	Cohort study	LC +OC, Western Australia Hospital Morbidity Data System.	20 084	1988-1994	All BDI (ICD screening > record review)	44 (+69 bile leaks)	57%	Adj OR 0.50 (0.35-0.70)
Z'Graggen et. al. 1998	Cohort study	LC, SALTS registry	10 174	1992-1995	Not stated	32	25%	NS

SALTS: Swiss Association of Laparoscopic and Thoracoscopic Surgery, LC: Laparoscopic cholecystectomy, OC: Open cholecystectomy, ICD: Identification through ICD codes, NS: Non significant

Questionable causality is a main issue with IOC-BDI research. It is likely, that some of the protective effect with IOC is not due to the procedure per se. Surgeons performing IOC on a routine basis may perform safer surgery during the whole procedure and IOC thus merely becoming a proxy for careful surgeons, less likely to cause careless injuries.
Flum et. al addressed this problem in their Medicare study[162]. Comparing routine versus selective IOC users regarding the incidence of BDI, routine surgeons had the lowest BDI rates, but only when they used IOC. When IOC was not used among routine users, the surgeons were at similar or even increased risk of injury as selective IOC users. However, the authors did not address the problem of unsuccessful IOC attempts, which is one of the major problems with administrative data that could potentially bias their result. The success rate of IOC varies, ranging from 66% to 98.9% in the before mentioned RCTs. As usually only successful IOC is registered with ICD-procedure codes, unsuccessful attempts due to generally difficult circumstances will be recorded as no IOC. A selection of difficult BDI-prone cholecystectomies will thus fall into the no IOC group, possibly explaining the increased BDI rate when routine users "chose" not to perform IOC.
Furthermore, some selective IOC users may only intervene with an IOC when a BDI has occurred, for injury confirmation prior to repair. This would cause a higher BDI rate in the IOC group, falsely diluting a possible protective effect.

These uncertainties, regarding the surgeons' different reasons for performing IOC are usually the main valid arguments against the protective effect reported in the majority of population-based studies.

It is evident that the IOC procedure in some cases may cause injuries[185], especially in the presence of inflamed, fibrotic, or short cystic ducts. Furthermore, IOC may be incorrectly interpreted and falsely convincing the surgeon of a normal anatomy[150]. To address this problem, some centres have adopted a routine of having radiologists interpreting the cholangiograms by telecommunication, allowing for real-time evaluation by dedicated experts.

Additionally, the main indication for IOC usage in the pre-laparoscopic era, detection of CBDS is still valid and should be kept in mind. In a Swedish study[56], 8% of patients with IOC during cholecystectomy were found to have CBDS, the majority being detected intraoperatively and thus not suspected preoperatively. Even though the clinical relevance of asymptomatic CBDS is unclear, this argument should be added to a possible protective effect against BDI whilst evaluating the pros and cons of IOC.

2.2.4.3.1 Intraoperative cholangiography and cost-benefit

The cost of an IOC varies depending on reimbursement system and the way it is calculated, ranging from $700[170, 177] to $100[186, 187]. In a cost-benefit analyses of IOC, Flum et. al.[188] calculated the difference in average costs of laparoscopic cholecystectomy with IOC ($8 649) to the average cost of laparoscopic cholecystectomy without IOC ($8 527) and concluded that IOC adds an average cost of $122 for IOC. Given the incidence numbers and mortality rates of BDI, the cost per life-year saved would be $13 900. Generally, interventions providing patients with one

life-year for less than $50 000, e.g. dialysis and seat-belts, are considered to be cost effective[189].

2.2.4.3.2 Alternatives to intraoperative cholangiography

A few alternatives to IOC have been suggested. The performance of a cystocholangiogram, through a catheter placed in the gallbladder has been shown to accurately delineate the bile tree and has been proposed as a safer alternative to IOC[190] .However, occlusive stones in the gallbladder pouch or cystic duct, not uncommon in acute cholecystitis, substantially limit the usefulness.
Laparoscopic ultrasonography has the advantage of noninvasively being able to demonstrate the biliary anatomy and possible CBDS at least as good as IOC[191-193] . However, the technique is very user dependent with need of ultrasonography skills. It is furthermore not readily available and is unlikely to become part of the toolbox of a general surgeon.

In conclusion, although substantial research efforts have been undertaken in order to evaluate a possible protective effect of IOC, the level of evidence is fairly poor. During recent years, quality registries with prospectively collected an validated data have the potential of addressing rare outcomes such as BDI with much more reliable estimates of incidence and effect of preventive actions such as IOC.

2.2.5 Diagnosis and treatment of bile duct injury

A BDI is discovered during the primary cholecystectomy (approximately 30%[194]), early after surgery or late, weeks to months after injury. A variety of treatment options are available ranging from simple draining to highly advanced reconstructive biliary and vascular surgery. It is important to do things right from start, and the early involvement of hepatobiliary expertise cannot be emphasized enough.

2.2.5.1 Peroperatively detected bile duct injury

If not discovered during IOC, a peroperatively suspected BDI should be confirmed with IOC if this can be performed safely[195]. Conversion and a subsequent primary repair should be performed by surgeons with experience in biliary reconstructive surgery, and further dissection, for confirmation of injury extent, should never be performed.

If no hepatobiliar expertise is available, it is preferable to not convert, insert a sub-hepatic drain laparoscopically and then refer the patient to a hepatobiliary unit for delayed repair. Primary repair by the same surgeon who caused the injury has been associated with poor outcome. Stewart and Way[195] reported only 17% successful repairs and Flum et. al.[2] reported an 11% increased mortality rate associated with repair attempted by the injuring surgeon.
The optimal strategy for an early repair still remains controversial. Small incisional injuries to the CBD or CHD are commonly repaired with direct closure and a T-tube. It may be successful but have also been reported to form strictures in almost every second

case[195]. Completely transected ducts require more extensive reconstructive surgery. End-to-end repair have been reported to be unsuccessful in the vast majority of cases[195], even though the early reported devastating results may be somewhat exaggerated[196]. The preferred reconstructive method is without doubts Roux-en-y hepaticojejunostomy, especially if the injury involves loss of ductal tissue or associated thermal or vascular injury. It is of great importance to delineate the extent of the injury and perform the anastomosis on vital, well vascularized ductal tissue, minimizing the risk of stricture formation within the anastomosis.

2.2.5.2 Postoperatively detected bile duct injury

Patients with postoperative symptoms as persisting pain, fever, nausea, jaundice or elevated laboratory findings (CRP, WBC and liver samples) should be evaluated with ultrasonography or abdominal CT, bearing a possible BDI in mind. A BDI not detected during the cholecystectomy may be revealed postoperatively either as a bile leakage and biloma or later, due to stricture formation, with jaundice and dilated bile ducts. The goal of the initial management is control of sepsis and on-going bile leakage with antibiotics and the placement of radiologically guided drains into fluid collections. Once biliary drainage has been achieved and sepsis controlled, it is often preferable to allow the local inflammation to resolve, usually for several weeks, before the definitive repair.

A cholangiogram, either by endoscopic retrograde cholangiography (ERC)[197] or percutaneous transhepatic cholangiography (PTC) is of fundamental importance prior to injury repair as attempts for such without a preoperative cholangiogram have been reported to be unsuccessful in 96% of the cases[195]. Moreover, cystic stump leakages and minor leakages from peripheral ducts in the liver bed can in the majority of cases be handled endoscopically by down-stream control with sphincterotomy or/and stent placement[198-200]. Additionally, ERC or PTC with dilatation and stenting is a treatment alternative when a BDI presents with jaundice due to stricture formation and with the bile ducts still in continuity. In a review of 159 BDI patients treated at the Mayo clinic, Rochester, Minnesota, USA, the success rate of endoscopic treatment was 99% for Strasberg A injuries. Of 66 obstructive Strasberg E1 to E4 injuries, 22 were attempted for endoscopic or percutaneous dilatation. Eleven of these patients were stented for a median time of 7 months, 8 with excellent result and 3 requiring surgical intervention[198]. The results show that endoscopic or percutaneous dilatation therapy of strictures is feasible in selected patients, but generally inferior to the success rate of surgical reconstruction with Roux-en-y hepaticojejunostomy. The latter being reported to have excellent results in 98% of 142 surgically repaired BDI patients at the Johns Hopkins Hospital, Baltimore, Maryland, USA[131].

2.2.5.3 Concomitant vascular injuries

Vascular injuries are commonly associated with BDI with incidence estimates approximating 25%[201]. The most common injury affects the right hepatic artery (>90%)[201], with isolated portal vein injuries and combined portal vein and arterial injuries being rare but with the addition of substantial complexity. The misinterpretation of the CBD being the cystic duct will result in a cranial dissection along the left side of the CBD/CHD with a subsequent division of the CHD in order to reach the cystic plate on which the gallbladder rests. The CHD is often divided at the location where the right hepatic artery passes under it. Mechanical or thermal trauma is usually the cause of damage to the vessel, or clips may be applied in the belief that it is the cystic artery. In an autopsy study, as many as 7% of patients having undergone cholecystectomy during their lifetime had an injury to the right hepatic artery or its branches[202]. It is evident that injuries to the delicate vascularisation of the bile ducts, often not obvious during the cholecystectomy, contributes to an upgrading of injury severity and could be a determinant of successful or unsuccessful repairs. A BDI in combination with injury to the right hepatic artery have been reported to be a predictor of restricture after BDI repair with cholangio-enteric anastomosis[127, 203, 204]. However, the timing of repair after concomitant vascular injury appears to be important. Attempts for an early repair are associated with a high rate of stricture development whereas delayed repairs had an excellent success rate[205], a difference probably explained by on-going ductal ischemia which have been reported to progress for about three months[97]. It has been suggested to routinely evaluate the arteries in patients with BDI when planned for early repair. If the right hepatic artery is occluded, the performance of a delayed repair, at least 3 months post injury, offers the best prognosis[201]. Injuries involving the portal vein or combined portal vein and arterial injuries are rare but can cause rapid liver infarction associated with excessive mortality. Such injuries require emergent referral to highly experienced hepatobiliar centres.

3 AIMS

The aims of this thesis are:

- To investigate the incidence of BDI in Sweden, using a National Quality Registry for Gallstone Surgery.

- To evaluate the long-term morbidity pattern after BDI, and to assess whether liver related diseases or cancer in the liver or bile ducts are overrepresented among injured patients.

- To estimate the mortality rate after BDI and investigate factors associated with increased mortality following BDI.

- To address the prevention of BDI by identification of risk factors, with special focus on acute cholecystitis and the use of intraoperative cholangiography.

4 PATIENTS AND METHODS

4.1 THE SWEDISH INPATIENT REGISTRY

Paper I and IV are based on data from the Swedish Inpatient Registry. Since 1965, the Swedish National Board of Health and Welfare collects data on individual hospital discharges in the Swedish Inpatient Registry. This registry is event based, and information on patient demographics, dates of admission and discharge, codes for discharge diagnoses, codes for surgical procedures, as well as hospital identification codes, are registered. The introduction of the registry was made by region, covering 10% of all hospital discharges in 1965 with an almost linear increase until 1987, when it reached full nationwide coverage. The degree of misclassification in the Swedish Inpatient Registry is low with a 94%, validated, agreement for surgical procedure codes[206].

4.2 THE SWEDISH REGISTRY FOR GALLSTONE SURGERY

The Swedish Registry for Gallstone Surgery and Endoscopic Retrograde Cholangiopancreatography (ERCP), GallRiks, was founded by the Swedish Surgical Society together with the Swedish Society of Upper Abdominal Surgery and the Swedish Society of Laparoscopic Surgery in 2005, and is financially supported by the Swedish national health authorities. Registration in GallRiks started in May 2005. The aim of the registry is to obtain a complete national registration of gallstone interventions and to provide continuously updated information regarding indications, treatment methods, and complications, as well as patient satisfaction with reference to the given treatment. GallRiks covers laparoscopic and open surgery of the gallbladder as well as endoscopic interventions of the bile ducts and pancreas, and uses an internet platform for online registration. The surgeon or endoscopist reports patient characteristics, indications, and choice of surgical method as well as detailed information of immediate complications. After 30 days, the medical records are reviewed and late complications reported by a local coordinator.

Since the registry's founding in 2005, the number of participating hospitals has steadily increased, and GallRiks is considered to be completely nationwide, including all Swedish centres performing biliary interventions, from 2009 and onwards. Comparison with data for registered cholecystectomies in the Swedish Inpatient registry, where all diagnosis codes and surgical intervention codes from the international classification of diseases (ICD) are registered, shows that the coverage rate has increased rapidly since the start of registration in 2005. The coverage rate was about 65% in 2006 and has steadily increased since. In 2009 and 2010, 90% of Swedish cholecystectomies were registered in GallRiks[207].

The data collected in GallRiks are validated on a regular basis by an independent audit group that regularly compares registered data with local patient records, both validating the data themselves as well as auditing to ensure that adequate resources

are assigned for registration and follow-up at each centre. Each hospital has been visited once every three years, and a sample of medical records is compared with entries of the registry database. GallRiks' annual report presents the results from hospital visits, and the review of the first 1207 medical records at 67 different hospitals showed 98% correct registrations[208].

4.3 PAPER I

4.3.1.1 Study design

A population based cohort study of all cholecystectomies within the Swedish Inpatient Registry in the period 1965-2005, aiming to assess survival, factors influencing survival and causes of death after reconstructed BDI.

4.3.1.2 Definition of bile duct injury cases

The study was limited to persons 15 years or older at the time of cholecystectomy. All cholecystectomies registered from 1965 through 2005 were identified (n = 391 937). Patients with inconsistent registry data were excluded (n=5879). Patients with malignant conditions possibly associated with the reconstruction (n=11 920) were identified using linkage to the Swedish National Cancer Registry. Moreover, 96 reconstructions referring to some benign biliary diagnoses and thus unlikely to be a result of BDI were also excluded. In order to define BDI cases, we selected those in the cholecystectomy population who during the index procedure, or within one year after it, had also undergone any reconstructive biliary procedure, excluding the above described cases.

4.3.1.3 Statistical analyses

Deaths and causes of death among study subjects were identified by linkage to the essentially complete Causes of Death Registry. In the cancer analyses, risk of cancer was estimated through linkage with the National Swedish Cancer Registry.

Survival among patients having undergone cholecystectomy, both with and without reconstructed iatrogenic BDI, was assessed firstly by the Kaplan-Meier method. Survival curves were then adjusted for age, sex and calendar period using a direct adjusted method based on a stratified Cox model[209].

The standardized mortality ratio (SMR), the ratio of the observed to the expected number of deaths, was used to estimate the relative risk of all-cause and cause-specific mortality, here specifically liver disease. The expected number of deaths occurring in the entire Swedish population was calculated by multiplying the observed person-time by age- (in five year groups), gender- and calendar year-specific mortality rates. The

SMRs are thus inherently adjusted for confounding by age at follow-up, gender and calendar year. Confidence intervals were calculated assuming that the observed number of events followed a Poisson distribution[209].

To compare survival of BDI versus non-BDI, a flexible parametric model was used to calculate Hazard ratio (HR) and 95% confidence interval (CI), with adjustments for sex, age at cholecystectomy, cholangiography and comorbidity.

Factors influencing survival were analysed using Cox proportional hazards regression models to calculate HR with 95% CI. The follow-up was from the date of reconstruction until December 31, 2005. Age was analysed as a continuous variable (yearly increase), calendar year as four categories (<1975, 1975-1984, 1985-1994 and 1995-2005) and method of reconstruction as two categories (direct suture repair and cholangio-enteric anastomosis). Comorbid diseases, other diagnoses at discharge from the reconstructive procedure hospital-stay that were not related to the procedure or complications of it were analysed using the Deyo modification of the Charlson comorbidity index[210, 211]. The diagnoses were weighted according to severity using the index and then grouped into Charlson score 0, 1 and ≥2, with the latter indicating the greatest comorbidity. Hospital type was defined as local, regional or university hospital level.

4.4 PAPER II

4.4.1.1 Study design

A population-based case control study on prospectively collected data from the Swedish Registry for Gallstone Surgery and ERCP, GallRiks, with the objective to determine factors linked to survival after cholecystectomy.

4.4.1.2 Definition of bile duct injury

BDI at cholecystectomy was defined as any tissue damage to the wall of any bile duct in the biliary tree, except for injuries to the gallbladder or the intended division of the cystic duct, detected during the cholecystectomy or diagnosed postoperatively as a result of bile leak or none-stone caused biliary obstruction. Specifically, all types of postoperative bile leaks, including leakage from the cystic duct, were included in this definition.

4.4.1.3 Statistical analyses

Available data of all 51041 cholecystectomies in GallRiks between May 1, 2005 and December 31, 2010 were extracted. The data included dates of death during the study period, collected from the National Population Registry.

Annual incidence rates of peroperatively detected BDI and those detected postoperatively (BDI with delayed detection), were calculated.

Survival among patients having undergone cholecystectomy, both with and without BDI, as well as by time of BDI detection, was assessed by the Kaplan-Meier method. In order to estimate the impact of BDI on survival, as well as to identify risk factors affecting survival, Cox proportional hazards regression was used to calculate HR with 95% CI. End point was all cause death. Sex, age, American Society of Anesthesiologists (ASA) classification, planned or emergency operation, hospital annual caseload, surgeon annual caseload, BDI and the use of IOC were introduced into the model as potential risk factors or confounders of survival. The proportional hazards assumption was examined using Shoenfeld's partial residuals[212]. The presence of BDI or not, sex, ASA-classification, planned or emergency operation and IOC did not completely fulfil the proportional hazards assumption and were entered in the model using the time varying covariate option for the main exposure variable and the strata option for potential confounders, i.e. by assuming different baseline hazard for each combination of those variables. The follow-up was from the date of cholecystectomy until date of death or end of follow-up on December 31, 2010. Age was analysed as a continuous variable (yearly increase) while comorbidity, measured using the ASA classification, was categorized as healthy (ASA 1), mild disease (ASA 2) or severely impaired health (ASA 3-5). The annual hospital caseload of cholecystectomies was dichotomized into low- or high-volume using the close to mean 200 annual cholecystectomies (mean=206, median=178). Surgeon annual caseload was similarly dichotomized into less or more than 14 (mean=21, median=14) annual cholecystectomies.

The use of IOC was dichotomized into performed or attempted IOC as one category and not attempted as the other, thus using an *intention-to-do* approach. In order to estimate the impact of IOC on BDI occurrence, a logistic regression model was used, adjusting for the same possible confounders as the cox model. Regarding missing data, the relative numbers were very low and handled by listwise deletion.

4.5 PAPER III

4.5.1.1 Study design

A population-based case control study of cholecystectomised patients within the Swedish Registry for Gallstone Surgery and ERCP, GallRiks, aiming for the investigation of risk factors for BDI.

4.5.1.2 Definition and classification of bile duct injury

In conformity with paper II, A BDI was defined as any tissue damage to the wall of any bile duct in the biliary tree, except for injuries to the gallbladder or the intentional division of the cystic duct. The injury may be detected during the cholecystectomy or

diagnosed postoperatively as a result of bile leak or non-stone caused biliary obstruction. Additionally, all types of postoperative bile leaks, including leakage from the cystic duct, were classified as BDI in this definition.

When sufficient information regarding injury extent and localization were available, the injuries were classified using the Hannover classification[99]. For severity grading, injuries commonly requiring reconstructive surgery with cholangio-enteric anastomosis, i.e. transectional or obstructive lesions to the common bile duct or common hepatic duct as well as lesions above the hepatic confluence were considered to be severe. Consequently, lateral incomplete injuries, cystic duct lesions and peripheral minor leaks from the gallbladder bed were considered as non-severe.

4.5.1.3 Statistical analyses

All cholecystectomies in GallRiks from May 1, 2005 to Dec 31, 2010 were included. Factors influencing the risk of BDI were analysed using multivariable logistic regression modelling. Each variable was tested univariably and multivariably according to purposeful selection as described by Hosmer and Lemeshow[213]. The models were tested for multicollinearity, effect modification and finally assessed using the Hosmer-Lemeshow goodness of fit test. The effects of analysed variables are presented as odds ratios (OR) for BDI with 95% CI.

Age was analysed as a continuous variable in the multivariable analysis, but also evaluated in categories (<40 years, 40-60 years and >60 years). Body mass index (BMI) could be calculated only for a subgroup of patients as this variable was introduced into the registry as late as 2010. BMI was categorized into underweight (BMI <18.5), normal (BMI 18.5-25), overweight (BMI 25-30) and obese (BMI >30) according to WHO definition[214]. Comorbidity was studied using ASA score, grouped as healthy (ASA 1), mild comorbidity (ASA 2) and severe comorbidity (ASA 3-5). The presence of acute cholecystitis or not is a specified variable within GallRiks and is determined by the reporting surgeon on clinical evidence, not by pathology report. Within the subgroup of patients with acute cholecystitis, the number of days from admission until surgery was used as a proxy for time of symptom onset to the time of operation and labeled cholecystectomy timing. Cholecystectomy timing was analysed as a continuous variable within the subgroup of patients with acute cholecystitis. The variables emergency/planned admission and acute cholecystitis were introduced into the model separately because they were collinear, but only the one representing the greatest confounding effect was retained in the model. The annual caseload of cholecystectomies was evaluated as a continuous variable in the regression models but presented categorized into low volume (< 10 per surgeon, < 100 per hospital), medium volume (10-40 per surgeon, 100-200 per hospital) and high volume (>40 per surgeon, >200 per hospital). The use of IOC was categorized into 1. Not intended, 2. Performed, 3. Intended but failed and finally 4. Intention to do (both performed and intended but failed together).

BMI was excluded from the multivariable model due to the amount of missing data BMI (>85%). For the remaining variables, the proportions of missing values were small. Missing values were therefore handled using listwise deletion.

4.6 PAPER IV

4.6.1.1 Study design

A matched, nested and population based case control study evaluating the impact of gallbladder inflammation on BDI risk.

4.6.1.2 Definition of cases and control

The study was limited to persons 15 years or older with a cholecystectomy performed between the years of 1990 to 2005. For practical purposes concerning medical record review, only cases and controls within the geographically restricted area of the five counties of the Lake Mälaren Valley in central eastern Sweden were included. Potential iatrogenic BDI cases were defined as a cholecystectomy with a procedure code representing biliary reconstruction within one year after removal of the gallbladder. To avoid other causes for biliary reconstruction, patients with a concomitant cancer diagnosis within two years of the index event or a diagnosis code representing a few benign conditions potentially treated with biliary reconstruction were excluded.

Control patients were defined as cholecystectomies without reconstructive biliary events, matched to cases on gender, age and year of cholecystectomy and randomly sampled to a case to control-ratio of 1:3.

4.6.1.3 Data collection

In accordance with the ethical approval, informed consent was sent out to living participants authorizing medical record review. Thirty-eight patients (10 cases and 28 controls) denied review.
Remaining cases´ and controls´ medical records were reviewed regarding patient and procedure related variables with hypothesized relation to BDI and gathered in a Microsoft Access® database.
With this procedure-code methodology, 50 potential BDI cases were wrongly identified as bile duct injuries and thus excluded. Furthermore, 14 potential cases and 45 controls were either inaccessible (due to deletion of patient records) or lacked sufficient information regarding surgery, injury extent or complications and were therefore excluded. Remaining cases and controls were included in the final analyses.

4.6.1.4 Acute cholecystitis and the 2013 Tokyo guidelines

The diagnosis of acute cholecystitis was made according to the 2013 revision of the Tokyo Guidelines for acute cholecystitis[41] (TG13). In order to meet the criteria of acute cholecystitis, the patient needs local signs of inflammation (Murphy's sign or right upper quadrant mass/pain/tenderness) as well as systemic signs (fever or elevated CRP/WBC count). According to TG13, a definite diagnosis of acute cholecystitis also requires a characteristic finding on imaging (ultrasound/CT/MRI). As the diagnosis of acute cholecystitis among cases and controls sometimes was made without imaging confirmation, the TG13 criteria of suspected diagnosis were used to define acute cholecystitis. Patients with acute cholecystitis were subsequently graded according to the TG13 severity assessment into mild (grade I), moderate (grade II) or severe (grade III).

4.6.1.5 Statistical analyses

As 147 of either cases or controls were excluded due to the above stated reasons, the loss of power caused by exclusion of incomplete pairs would have been considerable. This was handled by breaking the match and using unconditional logistic regression, controlling for the matched variables (age, gender, and year of cholecystectomy). Possible risk factors for BDI were tested univariably and multivariably using purposeful selection described by Hosmer and Lemeshow[213]. Age, BMI and CRP were treated as continuous variables in the models. BMI was presented as categorized into underweight (BMI < 18.5), normal (BMI 18.5-25), overweight (BMI 25-30) and obesity (BMI > 30) according to the WHO-definition[214]. BMI was not measurable in 29% of the patients, with missing values evenly distributed among cases and controls. The crude estimate of the effect of BMI on BDI was non-significant and BMI was thus not included in the multivariable model. Comorbidity was analysed using the Deyo modification of the Charlson comorbidity index[211]. The duration of symptomatic gallstone disease was estimated either from information available in the admission records or if missing, from a possible previous gallstone diagnosis in the Swedish Inpatient Registry. The time period was divided into three categories: symptomatic gallstone disease less than 1 year, 1-5 years or longer than 5 years. The duration of symptoms could not be found in 7% of the journals or records, and missing values was handled by listwise deletion. Due to significant collinearity between acute cholecystitis and emergency operation, these variables were analysed in separate models, and only acute cholecystitis was used for confounder adjustment. As CRP was not used on a regular basis during the early 1990^{ies} and usually only on patients with inflammation, 87% of elective cholecystectomies and 25% of patients with acute cholecystitis had missing values. The impact of CRP on BDI risk was thus investigated only in a subgroup of patients with acute cholecystitis and was not used for confounder adjustment. A Receiver Operating Characteristic (ROC) statistic was performed measuring the predictive value of CRP on BDI risk among patients with acute cholecystitis. The presence of CBDS was defined as suspected stone(s) on IOC. As the frequency of CBDS among patients without IOC (32%) was unknown, a subanalysis on patients with successful cholangiography data was performed. CBDS were subsequently not used for confounder adjustment.

The final models were tested for effect modification and assessed using Hosmer-Lemeshow goodness of fit test. OR for BDI were presented with 95% CI and p-values < 0.05 were considered to be significant.

5 RESULTS

5.1 PAPER I

A total of 374 042 cholecystectomies were identified during the years of 1965-2005. Among these, 1386 cases of iatrogenic BDI requiring surgical reconstruction within one year of the cholecystectomy were identified. A majority, 251 423 (67.5%) of the cholecystectomies, were performed in women, while 795 (57.4%) of the reconstructed BDI occurred in women. The mean age at the time of cholecystectomy was for all study subjects 52.6 years and for BDI cases 59.9 years

5.1.1.1 Long term survival after bile duct injury

The Kaplan-Meier survival curves showed an overall significantly lower survival among patients with reconstructed iatrogenic BDI compared to non-injured, with a one year mortality of 15,8% (Figure 5). After adjustments for age, sex and calendar year, survival in the BDI group was 9.8% (95% CI 8.7% - 10.9%) lower than that of patients without injury during the first year following operation, whereas long-term survival was similar. This change after adjustment was mainly due to the confounding effect of age.

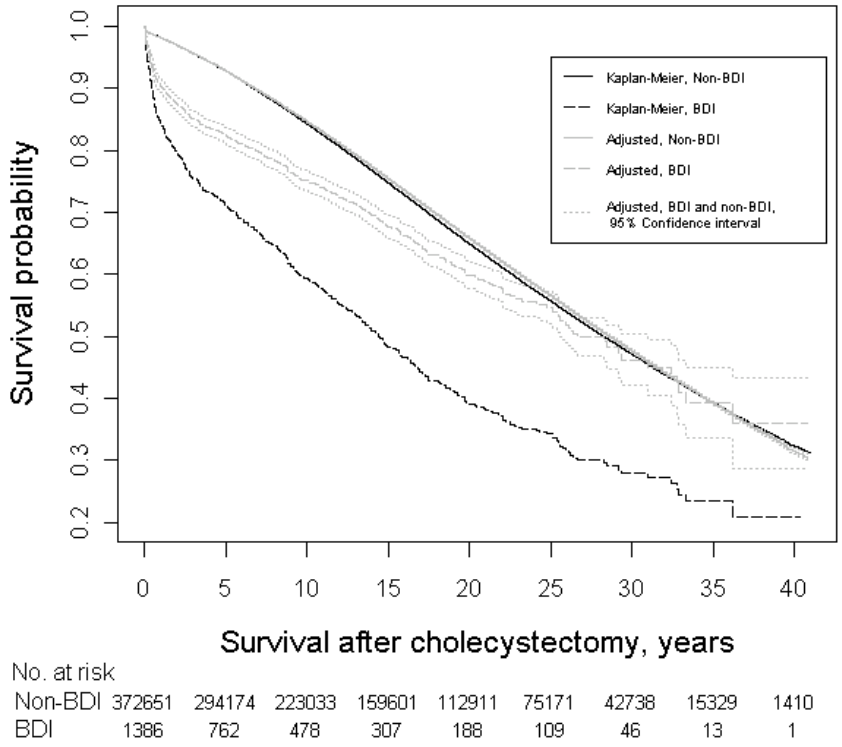


Figure 5. *Kaplan-Meier survival curves and survival curves adjusted for sex, age and calendar year of cholecystectomy for patients with and without reconstructed BDI.*

HR for death at three months, one, three and five years after cholecystectomy were 5.52 (95% CI 4.80-6.34), 3.73 (95% CI 3.30-4.22), 1.90 (95% CI 1.70-2.12) and 1.58 (95% CI 1.42-1.76), respectively among BDI patients. After seven years the relative risk gradually evened out.

5.1.1.2 Causes of death after bile duct injury

Within the first year after the cholecystectomy the overall adjusted SMR, was 7.39 (95% CI 6.42-8.47) for reconstructed BDI patients, compared to 1.45 (95% CI 1.41-1.48) in the non-injured group. The risk of dying from liver diseases of any kind in the BDI cohort was estimated to be 4.37 (95% CI 1.88-8.60) times that of the general population with cirrhosis of the liver 2.68 (95% CI 0.73-6.87) or cholangitis 62.9 (95% CI 17.1-161) as the most common registered causes of death (Table 5).

Table 5. *SMRs for all causes, as well as for hepatobiliary diseases among patients with or without BDI.*

		Non-BDI		BDI	
	Duration	**Observed**	**SMR[a] (95% CI)**	**Observed**	**SMR[a] (95% CI)**
All causes	Entire follow-up period	116,208	1.01 (1.00–1.01)	630	1.76 (1.63–1.90)
	<1 y	17,91	1.45 (1.41–1.48)	208	7.39 (6.42–8.47)
	1–4 y	6827	0.90 (0.89–0.92)	155	1.72 (1.46–2.01)
	>5 y	91,471	1.01 (1.00–1.01)	267	1.11 (0.98–1.26)
All liver diseases	Entire follow-up period	978	1.54 (1.44–1.64)	8	4.37 (1.88–8.60)
Cirrhosis	Entire follow-up period	876	1.42 (1.32–1.52)	4	2.68 (0.73–6.87)
Cholangitis	Entire follow-up period	38	2.00 (1.41–2.74)	4	62.9 (17.1–161)
Acute liver failure	Entire follow-up period	37	1.15 (0.81–1.59)	0	—

[a]The Swedish general population was used as a reference.

SMR, standardized mortality ratio.

SIR (Standardized Incidence Ratio, the observed number of cancers divided by the expected number) for cancer in the liver and bile ducts was 0.56 (95% CI: 0.51-0.61) among patients with cholecystectomy without BDI during the follow-up period compared to 1.61 (95% CI: 0.44-4.12) in the BDI group. As the expected number of cancer cases in the BDI group was very small (only 2.5) the cohort was too small for any analyses with acceptable precision.

5.1.1.3 Factors influencing survival after BDI

Sex did not appear to affect survival after BDI in the multivariate analyses, but there was a significant and gradual decrease in relative survival with increasing age at the time of injury. In comparing the defined calendar periods, no difference in survival after BDI was seen. The adjusted HR for death after reconstruction by cholangioenteric anastomosis, with suture reconstruction as the reference category, was 1.48 (95% CI, 1.23–1.79).

There was a dose-dependent association between increasing Charlson comorbidity score and the risk of not surviving after reconstructed iatrogenic BDI. No difference in survival was seen whether the reconstructive surgery was performed on the same date as the cholecystectomy, as in 85% of the cases, or on a later date, as in 15% of the cases. IOC was used in 780 (56%) of the 1386 cases of BDI. In the multivariate adjusted model, the use of an IOC indicated improved survival with a HR of 0.73 (95% CI, 0.62–0.86) compared with BDI cases in which IOC was not performed. Survival after reconstructed BDI was not affected by the hospital type where the reconstructive procedure was performed or by the hospital caseload of cholecystectomies at the hospital where the cholecystectomy was performed. Factors influencing the survival after BDI are displayed in Table 6.

Table 6. *Factors influencing the survival after reconstructed BDI.*

		Hazard Ratio for death after BDI	
	Frequency*	**Crude HR**	**Adjusted HR**
Gender			
Women	794	1.0 (reference)	1.0 (reference)
Men	590	1.56 (1.33-1.81)	1.07 (0.92-1.25)
Age			
per yearly increase	1384	1.08 (1.07-1.08)	1.07 (1.06-1.07)
Calendar year			
< 1975	112	1.0 (reference)	1.0 (reference)
1975-1984	294	1.24 (0.94-1.64)	0.81 (0.61-1.08)
1985-1994	380	1.60 (1.20-2.12)	0.93 (0.68-1.26)
1995-2005	598	1.30 (0.96-1.76)	1.09 (0.78-1.52)
Method of reconstruction			
Suture	585	1.0 (reference)	1.0 (reference)
Cholangio-enteric anastomosis	799	2.39 (2.01-2.83)	1.48 (1.23-1.79)
Comorbid diseases			
Charlson score = 0	508	1.0 (reference)	1.0 (reference)
Charlson score = 1	335	1.19 (0.93-1.53)	1.22 (0.94-1.60)
Charlson score >= 2	541	3.14 (2.54-3.87)	2.19 (1.75-2.75)
Reconstruction timing			
On the cholecystectomy date	1182	1.0 (reference)	1.0 (reference)
On a later date	202	0.60 (0.46-0.77)	0.82 (0.63-1.07)
IOC			
No	606	1.0 (reference)	1.0 (reference)
Yes	778	0.44 (0.38-0.52)	0.73 (0.62-0.86)
Hospital type			
University	301	1.0 (reference)	1.0 (reference)
Regional	437	0.94 (0.76-1.17)	1.00 (0.80-1.24)
Local	646	1.01 (0.83-1.23)	1.09 (0.87-1.36)
Hospital case load, per year			
>200	367	1.0 (reference)	1.0 (reference)
100-200	455	0.78 (0.65-0.95)	0.90 (0.73-1.11)
<100	562	0.84 (0.70-1.02)	0.87 (0.70-1.09)

* Two patients had cholecystectomies in 2005 and had reconstructions in 2006, which was after the end of follow-up (December 31, 2005), and were therefore excluded from further analysis.

5.2 PAPER II

Between May 1, 2005 and December 31, 2010, 51041 cholecystectomies were registered in the Swedish Registry for Gallstone Surgery and ERCP, GallRiks. In total, 747 BDI, were detected, corresponding to a cumulative incidence of 1.5%. There was no significant difference in BDI incidence between sexes, but the mean age of patients suffering an injury to the bile ducts was slightly higher, 55.2 years (95% CI 54.0 - 56.3), compared to non-injured, 50.7 years (95% CI 50.5 - 50.8).

A minority, 23% (170) of BDI, were detected and classified during the primary cholecystectomy whereas in 77% (577) detection was delayed, occurring in the postoperative period.

Annual distribution of registered cholecystectomies in GallRiks, together with peroperative and delayed detected BDI, are presented in Table 7.

Table 7. *Cholecystectomies and annual incidence of BDI in the Swedish Registry for Gallstone Surgery and ERCP, GallRiks.*

		BDI		
Year	**Cholecystectomies (n)**	**Early detection[a] (%)**	**Delayed detection[b] (%)**	**Total (%)**
2005[c]	1113	1 (0.1)	7 (0.6)	8 (0.7)
2006	7680	36 (0.5)	81 (1.1)	117 (1.5)
2007	8931	21 (0.2)	94 (1.1)	114 (1.3)
2008	10350	35 (0.3)	135 (1.3)	170 (1.6)
2009	11823	44 (0.4)	126 (1.1)	170 (1.6)
2010	11144	33 (0.3)	134 (1.2)	167 (1.5)
Total	**51041**	**170 (0.3)**	**577 (1.1)**	**747 (1.5)**

[a] BDI detected during cholecystectomy

[b] BDI detected after cholecystectomy

[c] May 1 - December 31 2005

5.2.1.1 Severity of bile duct injuries

Among severe BDI, 85% (n=41) were detected during the primary cholecystectomy. Among peroperatively detected lesions, 24% were correspondingly considered to be severe. A majority of BDI detected postoperatively were discovered as bile leakage, either from the cystic duct (46%) or from small ducts in the liver bed (18%), whereas only 2% (n=14) of injuries with delayed detection were considered to be severe.

5.2.1.2 Survival after cholecystectomy

The Kaplan-Meier survival curves show an overall significantly lower survival among patients with BDI compared to non-injured patients after cholecystectomy, with a one year mortality of 3.9% compared to 1,1% among non-injured. See Figure 6.

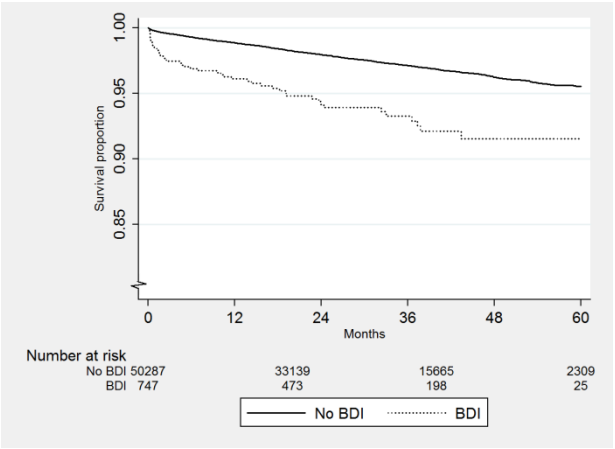


Figure 6. *Kaplan-Meier survival curve for patients with and without BDI*

Comparing peroperatively detected BDI, with delayed detected, the Kaplan-Meier survival curves show impaired survival in the delayed-detection group. Peroperatively detected injuries had a survival not differing significantly from that of non-injured subjects undergoing cholecystectomy. See Figure 7.

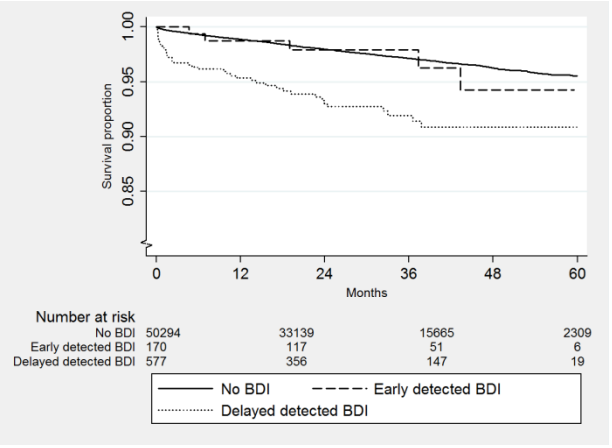


Figure 7. *Survival probability of patients after cholecystectomy in relation to no injury, early detected BDI and delayed detected BDI*

Analysing the cohort of patients suffering BDI with the Kaplan-Meier method, injured patients operated with the use, or attempt for use, of IOC had a significantly improved survival compared to injured patients where IOC was not attempted. See Figure 8.

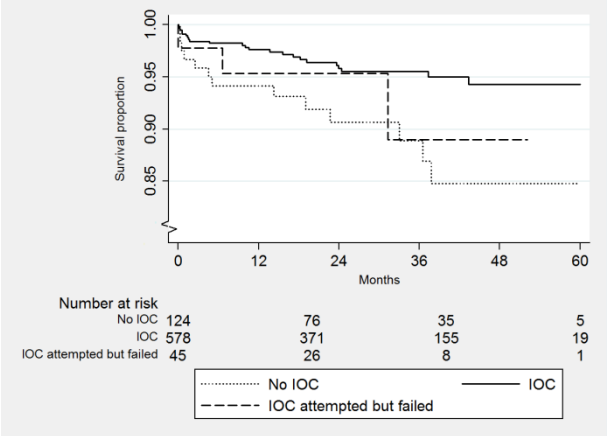


Figure 8. *Survival among patients suffering iatrogenic BDI during cholecystectomy, stratified according to the use of IOC or not.*

5.2.1.3 Factors influencing survival after cholecystectomy

The cox regression analysis showed a close to two-fold hazard of dying among injured patients compared to non-injured, during the first year (HR 1.92 95% CI1.24-2.97). When detection time was taken into consideration, injuries with delayed detection had a statistically significant approximately two-fold hazard of dying compared to non-injured (HR 1.95 95% CI 1.12-3.37). High age, increased ASA score and emergency operation were all associated to impaired survival after cholecystectomy in the multivariate model, whereas surgery at a hospital with annual cholecystectomy volumes of more than 200 was associated with improved survival.
The intention to use IOC significantly reduced the hazard of dying after cholecystectomy with 62% (HR 0.38 95% CI 0.31 – 0.46). See Table 8.

Table 8. *Cox proportional hazard model. Survival and factors influencing survival after cholecystectomy.*

		Hazard Ratio (95% CI)	
Variables		**Crude**	**Adjusted[c]**
Age (per yearly increase)		1.10 (1.09-1.10)	1.07 (1.07-1.08)
Sex	*Male*	1.0 (ref)	1.0 (ref)
	Female	0.48 (0.43-0.54)	0.85 (0.72-1.01)
ASA score*	*1*	1.0 (ref)	1.0 (ref)
	2	5.04 (4.29-5.92)	2.65 (2.11-3.34)
	3-5	23.46 (19.89-27.67)	9.76 (7.17-13.28)
Surgery*	*Planned*	1.0 (ref)	1.0 (ref)
	Emergency	2.49 (2.23-2.78)	2.05 (1.69-2.49)
Surgeon´s annual caseload[a]	*< 14*	1.0 (ref)	1.0 (ref)
	>14	0.89 (0.80-1.00)	0.90 (0.82-1.01)
Hospital annual caseload[b]	*< 200*	1.0 (ref)	1.0 (ref)
	> 200	0.77 (0.69-0.86)	0.86 (0.76-0.97)
Bile duct injury (BDI)*	*No BDI*	1.0 (ref)	1.0 (ref)
	BDI	2.57 (1.91-3.46)	1.92 (1.24-2.97)
	Early detection of BDI	1.17 (0.49-2.82)	0.71 (0.21-2.40)
	Delayed detection of BDI	3.02 (2.20-4.14)	1.95 (1.12-3.37)
IOC*	*Not performed*	1.0 (ref)	1.0 (ref)
	Performed	0.42 (0.37-0.48)	0.38 (0.31-0.45)
	Attempted but interrupted	0.51 (0.36-0.70)	0.36 (0.23-0.54)
	Intended	0.44 (0.38-0.50)	0.38 (0.31-0.46)

* Variables with sign of non-proportional hazards according to Schoenfeld residuals. Variables were thus treated as a time varying and the HR should be interpreted as the effect during the first year

[a] Median: 14 annual cholecystectomies/surgeon. A complementary analysis comparing high volume (more than 40 annual operations) to low volume (less than 10 annual operations) did not show significant survival differences, data not shown.

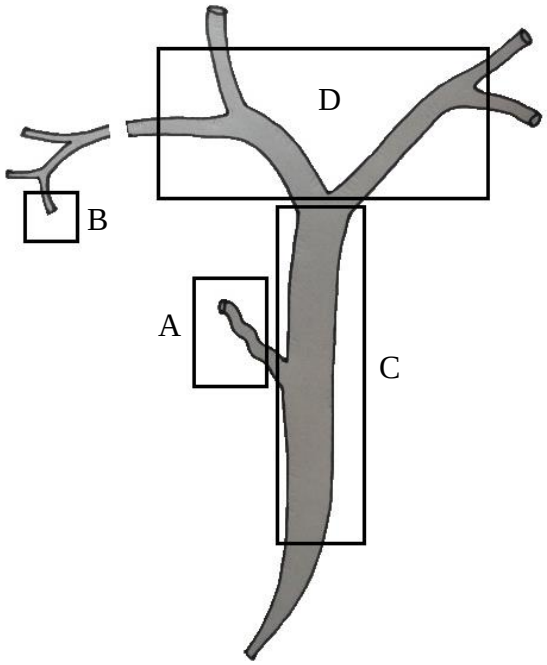
[b] Mean: 201 cholecystectomies/year

[c] Derived from a Cox regression model, mutually adjusted for variables listed in the table.

5.3 PAPER III

During the period May 1, 2005 to Dec 31 2010, 51 041 cholecystectomies were registered in GallRiks. Among these, 747 (1.46%) patients suffered an iatrogenic bile duct injury. The localization and extent of injuries are described in Figure 9. Of the 51 041 cholecystectomies 15 462 (30%) were operated under non-elective conditions and 9 008 (18%) were diagnosed with acute cholecystitis. There was a history of previous acute cholecystitis in 5787 of the operated patients (11%). Laparoscopic approach was used in 44 241 (90%) of the operations with a conversion rate of 9%. Patients with elective settings had a laparoscopic approach in 95% of the cases compared to 77% within the emergent surgery group.

Figure 9. *Distribution of 747 bile duct injuries among 51 041 cholecystectomies in GallRiks.*



Location	Type of injury	Hannover	N
A	Cystic duct lesion/leakage	A1	265
B	Lesion to peripheral ducts in the region of the gallbladder bed	A2	106
C	Tangential lesion of the common bile duct	C1, C2, C3	130
	Completely transected bile duct (at or below the hepatic bifurcation)	D1, D2, D3	16
	Obstructive injuries	B1, B2	7
D	Lesions above the hepatic confluence	C4, D4	32
	Injuries without sufficient information regarding location or extent.		191
		Total:	**747**

5.3.1.1 Risk factors for bile duct injury

There was no difference in the risk of BDI during cholecystectomy between men and women whereas increased age and comorbidity (represented by ASA-score) were independent and significant risk factors for injury. Among the subgroup of patients with data on BMI, there was no significant association between BMI and risk of BDI.

Table 9. *Odds ratio for BDI during cholecystectomy according to possible risk factors.*

	Odds ratio for bile duct injury at cholecystectomy	
Variable	**Crude**	**Adjusted[a]**
Age		
Per yearly increase	1.02 (1.01-1.02)	1.01 (1.01-1.02)
< 40 years	1.0 (ref)	1.0 ref
40-60 years	1.63 (1.32-2.00)	1.53 (1.24-1.89)
> 60 years	1.99 (1.62-2.44)	1.61 (1.28-2.02)
Sex		
Male	1.0 (ref)	1.0 ref
Female	0 .86 (0.74- 1.00)	0.95 (0.81-1.11)
BMI[b]		
Slim (BMI < 20)	1.03 (0.13-7.62)	0.85 (0.11-6.42)
Normal (BMI 20-25)	1.0 (ref)	1.0 (ref)
Overweight (BMI 25-30)	0.91 (0.60-1.40)	0.85 (0.55-1.31)
Obese (BMI <30)	0.92 (0.59-1.45)	0.91 (0.57-1.44)
ASA classification		
ASA 1	1.0 (ref)	1.0 ref
ASA 2	1.44 (1.24-1.68)	1.18 (0.99-1.40)
ASA 3-5	1.99 (1.56-2.53)	1.33 (1.01-1.75)
Admission		
Planned	1.0 (ref)	1.0 ref
Emergency	1.43 (1.23-1.66)	1.41 (1.21-1.64)
Surgical method		
Laparoscopic	1.0 (ref)	1.0 (ref)
Open	2.10 (1.74-2.54)	1.56 (1.26-1.94)
Acute cholecystitis		
No	1.0 (ref)	1.0 (ref)
Yes	1.40 (1.18-1.67)	1.23 (1.03-1.47)
History of cholecystitis		
No	1.0 (ref)	1.0 (ref)
Yes	1.54 (1.26-1.87)	1.34 (1.10-1.64)
Common bile duct stone(s)[c]		
No	1.0 (ref)	1.0 (ref)
Yes	1.62 (1.31-2.01)	1.51 (1.22-1.88)
Intraoperative cholangiography[d]		
Not performed	1.0 (ref)	1.0 (ref)
Performed	0.69 (0.57-0.85)	0.71 (0.58-0.87)
Attempted, but interrupted	1.13 (0.80-1.59)	1.14 (0.79-1.63)
Intention to do	0.71 (0.59-0.87)	0.76 (0.62-0.93)
Surgeon´s annual caseload		
Low volume (< 10)	1.0 (ref)	1.0 (ref)
Medium volume (10-40)	1.05 (0.90-1.23)	1.10 (0.94-1.28)
High volume (>40)	0.89 (0.70-1.13)	0.91 (0.71-1.18)
Hospital´s annual caseload		
Low volume (<100)	1.0 (ref)	1.0 (ref)
Medium volume (100-200)	1.15 (0.94-1.42)	1.03 (0.85-1.25)
High volume (>200)	0.99 (0.81-1.21)	1.10 (0.91-1.33)

[a] Adjusted for age (continuous variable), gender, ASA-classification, admission, acute cholecystitis, history of cholecystitis, surgical method, intraoperative cholangiography, surgeon´s caseload,(continuous variable) hospital´s caseload (continuous variable). All models showed satisfactory goodness of fit according to Hosmer and Lemeshow Goodness of fit test.

[b] Due to the large number of missing data was BMI not used in the multiadjusted model.

[c] Common bile duct stones detected during intraoperative cholangiography. Due to the relative large number of missing data (no successful cholangiography) and the subsequent risk of differential misclassification bias was common bile duct stones not used for confounder adjustment.

[d] Previously presented data: Törnqvist et. al. Effect of intended intraoperative cholangiography and early detection of bile duct injury on survival after cholecystectomy: population based cohort study, BMJ 2012;; 345:e6457

5.3.1.1.1 Acute cholecystitis and the risk of bile duct injury

Patients with acute cholecystitis had a 23% increased risk of BDI (OR 1.23 (95% CI 1.03-1.47)). Patients with a history of acute cholecystitis but no on-going inflammation at time of surgery were similarly at higher risk with OR for injury at 1.34 (95% CI 1.10-1.64) (Table 9). Compared with no cholecystitis, the odds ratio for severe and non-severe BDI associated with acute cholecystitis were 1.93 (95% OR 1.03-3.60) and 1.20 (95% CI 0.99-1.44), respectively (data not tabulated).

The risk of bile duct injury had an increasing, but non-significant trend, for every added day between admission and cholecystectomy among patients with acute cholecystitis, (p=0.38). When stratified by severity of the BDI the association with time since admission was attenuated and significant for severe injuries OR 1.15 (95% CI 1.01-1.31) but remained non-significant for non-severe injuries OR 1.01 (95% CI 0.94-1.09).

An intended IOC was associated with a 56% reduced risk of BDI among patients with on-going acute cholecystitis (OR 0.44 (95% CI 0.30-0.63)). Patients with a history of acute cholecystitis had a border significant risk reduction of 41% (OR 0.59 (95% CI 0.35-1.00)). Patients without a history of cholecystitis and without present acute inflammation did not have a risk reduction with the use of IOC (Table 10).

Table 10. *The effect of IOC intention among patients with and without acute cholecystitis.*

		Adjusted[a] odds ratio for BDI	
Peroperative condition	**IOC success rate**	***No IOC***	***Intention-to-do IOC***
Present acute cholecystitis	94.1%	1.0 (ref)	0.44 (0.30-0.63)
History of acute cholecystitis	96.1%	1.0 (ref)	0.59 (0.35-1.00)
No acute cholecystitis and no history of acute cholecystitis	97.8%	1.0 (ref)	0.97 (0.74-1.25)

[a] Adjusted for possible confounders using the same models as in table 9

5.4 PAPER IV

Using the methodology described in the method section, 232 cases of cholecystectomy with biliary reconstruction and 696 controls were identified within the defined catchment area study base. After collection of medical records, 158 BDI cases and 623 controls remained for statistical analyses.

Of the 158 reconstructed BDI cases, 10.8% (n=17) were complete transections of the CBD or CHD. 15.8% (n=25) of the injuries were transections or major tangential injuries to bile ducts above the hepatic confluence. A majority, 68.9% (n=109), of the injuries consisted of lateral incomplete lesions to the CBD or CHD. Nine injuries (6%) had a peroperatively discovered concomitant vascular injury to the right hepatic artery. A majority, 80%, of the injuries were discovered during cholecystectomy with the remaining discovered at a median of 7 days post cholecystectomy (range 1-250 days). A detailed description of BDI pattern, classified according to the Hannover classification is presented in table 11, and characteristics among cases and controls in table 12.

Table 11. *Distribution of BDI according to the Hannover classification.*

Hannover classification	N (with vascular injury)
Peripheral leakage	
A1 - Cystic duct leak	2
A2 - Leak in the gallbladder bed	0
Biliary tract occlusion	
B1 - Incomplete	3
B2 - Complete	0
Tangential injury	
C1 - Lesion < 5 mm	73 (1)
C2 - Lesion > 5 mm below hepatic confluence	34 (1)
C3 - Extensive lesion at hepatic confluence	2
C4 - Extensive lesion above hepatic confluence	11 (2)
Complete transection	
D1 - Without defect below hepatic confluence	6
D2 - With defect below hepatic confluence	7 (2)
D3 - At hepatic confluence	4 (1)
D4 - Above hepatic confluence	14 (2)
Late stenosis	
E1 - Main bile duct, short < 5 mm	0
E2 - Main bile duct, > 5 mm	2
E3 - At hepatic confluence	0
E4 - Above hepatic confluence	0
Total	**158 (9)**

Table 12. *Characteristics of cases and controls.*

Variable	Cases (N=158)	Controls (N=623)	*Missing values*
Gender[a]			*0*
Male (%)	75 (47%)	309 (50%)	
Female (%)	83 (53%)	314 (50%)	
Age[a]**, mean (SD)**	58.6 (16.5)	61.3 (15.7)	*0*
BMI, mean (SD)	27.2 (4.40)	26.3 (4.19)	*229*
Comorbidity (Charlson index)			*0*
0	84 (53%)	435 (70%)	
1	30 (19%)	103 (17%)	
2	44 (28%)	85 (13%)	
Years with gallstone disease			*55*
>1 years (%)	46 (29%)	253 (41%)	
1-5 years (%)	52 (33%)	239 (38%)	
> 5 years (%)	44 (28%)	92 (15%)	
Cholecystectomy settings			*0*
Laparoscopic (%)	130 (82%)	499 (80%)	
Open (%)	28 (18%)	124 (20%)	
Emergency (%)	61 (39%)	166 (27%)	
Planned (%)	97 (61%)	457 (73%)	
Acute cholecystitis (%)	40 (25%)	104 (17%)	
CRP[b]*, mean (SD)*	163 (91)	121 (95)	*590*[b]
CRP < 10	1 (3%)	4 (5%)	
CRP 10 - 100	9 (30%)	38 (49%)	
CRP > 100	20 (67%)	36 (46%)	
Acute cholecystitis in the medical history (%)	40 (25%)	92 (15%)	*0*
Acute pancreatitis (%)	3 (2%)	15 (2%)	*0*
Acute pancreatitis in the medical history (%)	16 (10%)	60 (10%)	*0*
Common bile duct stones (%)	15 (13%)	47 (11%)	*251*[c]
Intraoperative cholangiography (IOC)			*0*
No (%)	30 (19%)	184 (29%)	
Yes (%)	120 (76%)	410 (66%)	
Attempted, but failed IOC (%)	8 (5%)	29 (5%)	
IOC To confirm BDI[d] *(%)*	29 (18%)	*	
IOC intention[e] *(%)*	99 (62%)	439 (70%)	

[a] Matching variables

[b] CRP among patients with acute cholecystitis (36 missing values in this group)

[c] Patients without conclusive IOC

[d] IOC (to confirm BDI) after complete division of suspected cystic duct

[e] Intention to do IOC, consists of: performed IOC and attempted but failed IOC but not cases where IOC was used to confirm BDI.

5.4.1.1 Severity of acute cholecystitis and the risk of bile duct injury

Among the BDI cases, 25% (n=40) had on-going acute cholecystitis. The corresponding figure among controls was 17% (n=104). The severity distribution of acute cholecystitis among cases and controls, according to the Tokyo guidelines (TG13), are presented in table 13.

Table 13. *Severity assessment according to the 2013 Tokyo Guidelines.*

Tokyo grade for acute cholecystitis	Cases	Controls
Mild (grade I) Does not meet the criteria of grade II or III	13	53
Moderate (grade II) Associated with any one of the following conditions: 1. Elevated WBC count (>18 000/mm^3) 2. Palpable tender mass in the right upper abdominal quadrant 3. Duration of complaints >72 h 4. Marked local inflammation	25	49
Severe (grade III) Associated with dysfunction of any one of the following organs/systems 1. Cardiovascular dysfunction (Hypotension requiring treatment with dopamine <5 μg/kg per min, or any dose of norepinephrine 2. Neurological dysfunction (decreased level of consciousness) 3. Respiratory dysfunction (PaO2/FiO2 ratio <300) 4. Renal dysfunction (oliguria, creatinine >2.0 mg/dl (>180 μmol/L)) 5. Hepatic dysfunction (PT-INR > 1.5) 6. Haematological dysfunction (platelet count <100 000/mm^3)	2	2

The adjusted risk of BDI was close to doubled among patients with on-going acute cholecystitis (OR 1.97 95% CI 1.05 to 3.72). Furthermore, patients with a former diagnosis of acute cholecystitis had more than three times the risk of a BDI in the subsequent cholecystectomy compared to patients without a former cholecystitis diagnosis (OR 3.63 95% CI 2.00 to 6.57). Increased severity of acute cholecystitis was associated with a corresponding increase in injury risk. Whereas a mild acute cholecystitis (Tokyo grade I) did not significantly increase the risk of injury (OR 0.96 95% CI 0.41 to 2.25), a moderate cholecystitis (Tokyo grade II) more than doubled the risk (OR 2.41 95% CI 1.21 to 4.80). Additionally, a trend towards even higher risk was seen among the most severe cases of acute cholecystitis (OR 8.43 95% CI 0.97 to 72.9).

Within the acute cholecystitis group, CRP showed a linear trend with a small increase in injury risk corresponding to an increase of one unit of CRP. The ROC - area under the curve regarding CRP was 0.64 (data not shown).

The detailed results of the multivariate regression are listed in table 14.

Table 14. *Logistic regression with odds ratios for reconstructed BDI at cholecystectomy.*

		Odds ratio for BDI (95% CI)	
Variable		**Crude**	**Adjusted[a]**
Gender		*	*
Age		*	*
BMI	*per unit increase*	1.04 (0.99-1.10)	1.02 (0.97-1.08)[b]
	Underweight (BMI < 18.5)	1.21 (0.13-11.2)	1.67 (0.16-18.1)[b]
	Normal (BMI 18.5-25) (ref)	1.0 (ref)	1.0 (ref)
	Overweight (25-30)	1.25 (0.78-2.02)	1.25 (0.73-2.12)[b]
	Obese (BMI > 30)	1.73 (0.98-3.06)	1.53 (0.82-2.88)[b]
Comorbidity (Charlson index)			
	0 (ref)	1.0 (ref)	1.0 (ref)
	1	1.90 (0.72-1.49)	1.70 (0.85-3.38)
	2	3.77 (2.33-6.08)	3.71 (1.96-7.01)
Years with gallstone disease			
	<1 years (ref)	1.0 (ref)	1.0 (ref)
	1-5 years	1.21 (0.78-1.88)	1.24 (0.70-2.21)
	> 5 years	2.96 (1.80-4.88)	2.88 (1.51-5.48)
Cholecystectomy			
	Laparoscopic (ref)	1.0 (ref)	1.0 (ref)
	Open	0.95 (0.60-1.51)	0.93 (0.47-1.84)
	Planned (ref)	1.0 (ref)	1.0 (ref)
	Emergency	1.88 (1.29-2.74)	2.62 (1.46-4.72)
Acute cholecystitis			
	No (ref)	1.0 (ref)	1.0 (ref)
	Yes	1.94 (1.25-2.99)	1.97 (1.05-3.72)
	Tokyo grade I (mild)	1.22 (0.63-2.33)	0.96 (0.41-2.25)
	Tokyo grade II (moderate)	2.59 (1.51-4.43)	2.41 (1.21-4.80)
	Tokyo grade III (severe)	5.26 (0.72-38.58)	8.43 (0.97-72.9)
	CRP (per unit increase)	1.01 (1.00-1.01)	1.01 (1.00-1.01)[c]
Acute cholecystitis in the medical history		2.12 (1.38-3.26)	3.63 (2.00-6.57)
Acute pancreatitis		0.83 (0.24-2.92)	1.76 (0.41-7.52)
Acute pancreatitis in the medical history		1.09 (0.61-1.96)	1.13 (0.50-2.59)
Common bile duct stones		0.99 (0.59-1.66)	0.79 (0.39-1.61)[d]
Intraoperative cholangiography			
	No intention	1.0 (ref)	1.0 (ref)
	Yes intention	0.68 (0.47-0.99)	0.48 (0.29-0.81)

* matching variables

[a] adjusted for age, gender, comorbidity, years with gallstone disease, laparoscopic or open cholecystectomy, Tokyo grade of acute cholecystitis, history of acute cholecystitis, acute pancreatitis, history of acute pancreatitis, and IOC.

[b] Subgroup analysis, BMI was not used for confounder adjustment due to large number of missing values.

[c] Subgroup analysis among patients with acute cholecystitis. CRP was not used in the multivariable models due to the large number of missing values.

[d] Subgroup analysis, common bile duct stones was not used for confounder adjustment due to the missing data of operations without IOC.

6 DISCUSSION

6.1 METHODOLOGICAL ASPECTS

6.1.1 Paper I

The population-based design with objectively collected administrative data on a vast majority of the cholecystectomies performed in Sweden during the study period and the essentially complete follow-up evaluation of cohort members is a major strength of this study. Even though the large sample-size to a large extent minimizes random errors and thus improves precision, some important remarks regarding the validity, i.e. potential systematic errors (bias), of the study need to be clarified.

The population based design using the whole cohort of cholecystectomised patients minimizes the risk of selection bias and makes it well representative for the general population. However, some concern may be appropriate because several of the major university hospitals joined the Swedish Inpatient Registry rather late and BDI occurring at local hospitals but reconstructed at these referral hospitals were consequently not registered. This might reflect the rather low BDI incidence in the early part of the study period and possibly cause an overrepresentation of less severe BDI cases without the need of referral within the early years of the registry. This might partly explain the lack of improved survival, comparing different time periods, which would be anticipated given the improvement in handling surgical complications during the more recent time periods.

Questions may also be raised regarding the identification of BDI and the risk of misclassification bias. Firstly, interpreting the results, it is important to keep in mind that identification of BDI through ICD-procedure codes for cholecystectomy with a subsequent biliary reconstruction only identifies a subgroup of patients with major BDI, as minor injuries usually can be handled by less invasive means[198-200]. The degree of misclassification of ICD-procedure codes have been shown to be as low as 2%, compared to the much more unreliable registration of diagnosis and complication codes[206]. Secondly, and of fundamental importance when it comes to survival analyses, it requires a complete identification of underlying malignant conditions in the hepato-biliary tract, not uncommonly associated with reconstructive biliary surgery and with the potential of severely influence the survival. Previous research, using this methodology for BDI identification within administrative data[120, 162, 183], claims to exclude possible malignancies although without stating if this identification was made on ICD-diagnosis codes. Russel et.al. used this methodology of BDI identification concluding only 47 of 175 possible BDI to be major injuries requiring reconstruction. The other 128 cases were minor BDI or *malignant* conditions not excluded by the used algorithm, the relative frequencies unfortunately not declared. As diagnostic ICD-codes have been shown[215] to be an unreliable source for malignancy identification, in paper I, the identification of these patients was based on linkage with the 98% complete Swedish National Cancer Registry[216] excluding subjects who previously, or within one year after the cholecystectomy had been diagnosed with a cancer in the upper gastrointestinal tract.

In a study of this size, it was not possible to perform a manual review of the medical records and thus the risk of remaining misclassification bias cannot be completely disregarded.

The survival analysis requires a complete follow-up and identification of censoring. The use of the individually unique national registration number permitted linkage of information across several registries. By linkage with the essentially complete Causes of Death Registry, we identified all death events among cohort members from the start of follow-up until death, emigration, or the end of the follow-up period (December 31, 2005). Dates of emigration were obtained through record linkage to the National Registry of Emigration.

One intention of the study was to evaluate if the incidence of cancer in the liver or bile ducts was increased after BDI. However, due to the relative rareness of these cancers, statistically well powered comparisons of the Standardized Incidence Ratio (the observed number of cancers divided by the expected number) was not possible.
An important type of bias in epidemiological studies is confounding. In the Cox model, we have controlled for the possible confounding effect of sex, gender, calendar period, comorbidity, method of reconstruction, reconstruction timing, IOC, hospital type and hospital caseload. However, there are possible confounders that we have not been able to control for. We have not been able to control for severity of the gallstone disease, the presence of inflammation or surgeon factors, all potentially influencing the survival. The severity of the gallstone disease and acute or chronic cholecystitis could not be determined with sufficient reliability and the identity of the surgeon is not among the registered variables within the Inpatient Registry. Moreover, the IOC registration is possibly biased by the inability to detect unsuccessful attempts for IOC not accompanied by an ICD code, with a subsequent overrepresentation of difficult cases in the non IOC-group. The reason for IOC usage could also not be clarified; IOC might be used to prevent BDI or to detect BDI, a matter of fundamental importance when interpreting the results.

Finally, as the ICD code for laparoscopic cholecystectomy was introduced late in Sweden, and only gradually came to be used widely, it was not possible to distinguish reliably between laparoscopic and open cholecystectomies and consequently we did not stratify our risk factor analyses by open or laparoscopic procedure.

6.1.2 Paper II

The major strength of this study is the population-based design, with prospectively collected data from GallRiks, From the start of the registry in May 2005, a continuous validation process has disclosed a high validity of registered data. Annual reports deal with coverage and accuracy of registered data, and present web-based summaries that are easily available to participating hospitals and the community at large.

Self-reported registries are always prone to a risk of selection bias, in which the reporting clinician might fail to report negative events related to the intervention,

thereby generating a falsely low rate of complications. To minimize losses in validity by data being self-reported in GallRiks, a local non-physician coordinator at each hospital reviewed complications and interventions 30 days after surgery. The review would look at pharmacological treatment, percutaneous drainage, endoscopic interventions, or reoperations.

There might be some concern about how we used data at the start of the registry, even though the registry did not have nationwide coverage until 2009. However, the annual reports showed that data were valid, even for registration early in the period. Moreover, the risk of selection bias imposed by low coverage was largely relieved by the fact that coverage, even in the registry's early years, was high at each participating hospital, and that the increased coverage during the period 2005-2009 has predominantly been by the addition of new hospitals and not by a gradual increase in coverage within each hospital. Since the Swedish healthcare system is largely based on hospitals with defined catchment areas, it is reasonable to consider the registry to be population based from the start of registration, since coverage has always been high within each catchment area.

A study validating registrations of complications in GallRiks was presented in the registry's annual report of 2010, comparing registration in the Swedish health insurance system with GallRiks data. All health related injuries associated with a cholecystectomy reported to the insurance system between 1 June 2005 and 31 May 2010 were cross checked with GallRiks. All cases of BDI reported to the Swedish patient insurance were also documented as a BDI in GallRiks, indicating a good coverage of these cases in the registry throughout the study. Furthermore, 90% of cholecystectomies in the Swedish Inpatient Registry were also registered in GallRiks. Another strength of this study was the ability to detect the entire spectrum of injuries, ranging from less severe bile leakages after surgery (such as leakages from the cystic duct or lesions to peripheral ducts in the liver bed) to severe injuries (with transections with or without tissue loss located at or above the hepatic confluence). The vast majority of studies on this topic have focused either on major BDI, referred to and treated by tertiary hepato-biliary centres, or a selection of cases accessible to endoscopic treatment. Larger, population based studies originating from administrative national registries with injury identification through ICD diagnosis or procedure codes have substantial difficulties with the identification of less severe bile duct injuries, owing to the inconsequent registration of complication codes. A detailed registration of localization and extent of detected lesions in GallRiks enables a classification of injuries according to existing international classification systems.

Unfortunately, data for concomitant vascular injuries were not registered in GallRiks, which could have understaged the severity of combined BDI and vascular injury, since the frequency of such injuries can be estimated to occur in approximately 25% of BDI[201].

There also might be arguments against including minor, postoperative bile leakages into the definition of BDI, since these are often managed conservatively, and only a minority of these leakages have been properly diagnosed and therefore eligible for bile duct injury classification. These injuries are rarely included in published incidence data

of BDI, although they are clearly defined as bile duct injuries in the majority of internationally accepted classification systems. Furthermore, even cystic duct leaks and small peripheral injuries cause bile leaks and have the potential of causing biliary peritonitis. It is thus highly relevant to include these minor BDI in research aiming at complication prevention.

In the survival analysis using a Cox model, a few variables, listed in the method section, did not completely fulfil the proportional hazard assumption. To deal with this a stratified Cox models using a time varying covariate for the main exposure variables were used. Thus, the effect of these variables should be interpreted as the influence on survival during the first year after the cholecystectomy. In other words, the effect of these variables on survival varies over time. It is furthermore important to keep in mind that the follow-up is relative short and the excessive mortality seen within the study most likely represents post-operative complications rather than late complications due to stricture formation and recurrent episodes of cholangitis.

The variables; emergency or planned admittance and the presence of acute cholecystitis or not were highly collinear. To handle this, only the variable representing the greatest confounding effect, emergency or planned admittance, was kept in the Cox model.

A major advantage of the GallRiks registry is the IOC coding, identifying not only successful cholangiograms but also unsuccessful attempts. The inability to detect these failed attempts has been a major source of uncertainty within previous studies of the possible preventive effect of IOC. The reasons for the IOC are however still not known and this study setting cannot address the question regarding a safe surgeon effect.

6.1.3 Paper III

The methodological remarks of paper II, with regards to the validity and potential shortcomings of the GallRiks registry is comparable to this paper as the study base and BDI identification methodology are identical.

There is no globally accepted gold standard classification of BDI. The Strasberg[97] classification is perhaps the most commonly used but lacks information about vascular injuries. The more recent, Hannover[99] classification is more detailed than the Strasberg classification, including vascular lesions and transferable. Concomitant vascular injuries are unfortunately not registered in GallRiks, potentially underestimating the severity of a BDI as the addition of a vascular component may influence and complicate even small ductal lesions. When sufficient information regarding injury extent and localization were available, we have classified injuries using the Hannover classification. For severity grading, injuries commonly requiring reconstructive surgery with cholangio-enteric anastomosis, i.e. transectional or obstructive lesions to the common bile duct or common hepatic duct as well as lesions above the hepatic confluence were considered to be severe. Consequently, lateral incomplete injuries, cystic duct lesions and peripheral minor leaks from the gallbladder bed were considered as non-severe. McMahon et. al[100] proposed a definition of

major and minor BDI where lacerations > 25% of the bile duct diameter, transections of the CBD or CHD or postoperative strictures were considered as major injuries. Lacerations < 25% of diameter or lacerations of the cystic duct-CBD junction were considered as minor. Our definition is similar to this with a few exceptions; We have chosen to consider lateral incomplete injuries below the hepatic confluence as non-severe as these commonly are addressed without cholangio-enteric anastomosis. Furthermore, cystic duct leaks and peripheral leaks, not mentioned by McMahon are considered as less severe. Analyses addressing the severity using our definition or McMahon's did not differ significantly (data not shown).

The proportion of lesions without sufficient information for injury classification may seem high (191 of 747), but these are mainly postoperatively detected bile leaks discovered during the 30 day follow-up and the lack of injury classification is mainly due to limited clinical work-up rather than flawed registration.

The GallRiks registry does not confirm the diagnosis of acute cholecystitis by histological report, and it is based upon clinical evidence and reported by the surgeon. This is a potential weakness as one might be concerned that the reporting of acute cholecystitis might be biased as surgeons causing an injury could be more likely to report generally difficult circumstances. However, analysing the subgroup of patients with BDI detected after the date of cholecystectomy, when the surgeon had already reported pre- and peroperative data without the knowledge of an injury, a similar risk effect of acute cholecystitis was seen (data not shown).

One may argue that analyses of an association between IOC and BDI risk should not include minor injuries such as cystic duct leaks and peripheral ductal/Lushka leaks. However, possible associations between minor injuries and IOC include prevention of leaks from the cystic stump and minor peripheral lesions by the discovery, and subsequent handling of CBDS. The frequency of peroperatively detected CBDS among patients with a BDI was 18%. This rate is significantly higher than that of 12% in the whole cohort, a finding supported by previous research[199], strengthening the hypothesized causality between retained CBDS and minor injuries/leakages. Another reason for including cystic duct leaks/lesions in IOC research is that one of the arguments against the use has been that cystic duct cannulation may in fact cause injuries to the cystic duct with a subsequent higher risk of postoperative leakage[187].

As mentioned previously, one of the drawbacks of the GallRiks registry is that the reason for performing/not performing IOC cannot be clarified. We are unable to control for the safe-surgeon-factor. It is possible, and even likely, that a part of the protective effect of IOC is due to that some cholangiography-users are more likely to perform "safe surgery". These surgeons might have reduced complication rates caused by a generally safe approach, rather than having a protective effect by the cholangiography per se. Flum et. al.[162] addressed the safe surgeon effect and concluded that surgeons performing IOC in more than 75% of their cholecystectomies had increased BDI rates when IOC was not used. However, this BDI and IOC data could not detect failed, BDI prone, attempts for IOC possibly explaining the whole difference.

6.1.4 Paper IV

One of the strengths of this study is the population-based design. The study base, with all cholecystectomies performed in the area of eastern mid-part of Sweden 1990-2005, allows for identification of a relatively large number of cases despite the rareness of iatrogenic BDI. BDI identification through ICD procedure codes for surgical biliary reconstruction identifies only major injuries as minor injuries in particular may successfully be addressed by other means, such as interventional endoscopy. Those injuries will not be detected using this method, thereby restricting external validity, i.e. generalizability, to major biliary lesions.

A case–control study offers advantages in research concerning rare outcomes, such as iatrogenic BDI. When detailed information regarding the surgical procedure or patient characteristics are lacking in registries, a case-control study with review of medical records is often the only cost-effective solution. On the other hand, the process of reviewing medical records may introduce information bias due to incomplete medical records which is a weakness in this study design.

As falsely identified BDI cases and incomplete records were excluded, a conditional logistic regression with pair matched cases and controls would result in significant loss of power due to the exclusion of incomplete pairs. The solution of this problem was to break the match and subsequently analyse the data as frequency matched, controlling for the matched variables in unconditional logistic regression models. The loss of precision, using unconditional regression instead of conditional logistic regression was well compensated by the gained power of including all BDI cases.

The review of the medical records enabled a detailed severity grading of patients with acute cholecystitis. The severity grading according to Tokyo Guidelines have the advantage of being easily determined in the clinical setting. It is furthermore globally accepted and offers favourable conditions regarding comparability of research.

Regarding variable selection, the appearance of the gallbladder was not used for confounder adjustment, although generally available in the surgeon's report. Undoubtedly interesting, this finding is however possibly strongly biased by the fact that surgeons causing BDI are likely to emphasize difficult circumstances like chronic cholecystitis in the postoperative report. The frequency of pathology reports was unfortunately too low for analyses with acceptable precision making the duration of gallstone disease the most reliable proxy for the impact of chronic cholecystitis.

With this study setting, we were able to get detailed information regarding the use of IOC. We have continued to use the intention-to-do approach, adding failed attempts of IOC to the intended group. Moreover, some surgeons only used IOC to confirm and evaluate the extent of a suspected iatrogenic BDI causing an apparent high incidence of injuries in the cholangiography group. A thorough review of the surgical reports made it possible to identify operations where the cholangiography was used solitarily for BDI confirmation, after division and clipping of a suspected cystic duct, subsequently falling into the no-intention group.

6.2 FINDINGS AND IMPLICATIONS

6.2.1 Incidence of bile duct injury

Analysing data from the Swedish Registry for Gallstone Surgery, GallRiks (study I and II), we found a BDI incidence of 1.46%, with the majority (77%) being detected postoperatively. This exceeds by far the previously reported incidence figures averaging 0.25% in the era of open cholecystectomy and 0.55% after the introduction of the laparoscopic technique. The explanation for this is GallRiks ability to identify the whole spectrum of injuries, ranging from cystic duct leaks and minor peripheral ductal leaks to major injuries with complete transection of major ducts with tissue loss. If we restrict to major injuries requiring repair by cholangio-enteric anastomosis, the incidence drops to 0.11%, well comparable to the lowest incidence figures based on ICD-procedure codes of biliary reconstruction. It is thus obvious that the majority of BDI comprises minor and moderate BDI, not accurately measurable with the ICD-code methodology. As stricture development may take time, and GallRiks follow-up is limited to 30 days postoperatively, it is likely that the true incidence of BDI is even larger than presented here. Nevertheless, this incidence figure is probably among the most accurate estimate of BDI after cholecystectomy emphasizing the need of prevention and early diagnostic efforts when patients do not follow the expected recovery.

6.2.2 Health consequences of bile duct injury

The results of study I and II confirms the impaired survival after BDI reported by previous authors. In study I, surgically reconstructed BDI had a one-year survival of 9.8%, corresponding to an adjusted HR for death 3.7 times that of non-injured. In study II, analysing survival in the GallRiks registry, with shorter follow-up period, one-year mortality after BDI (minor and major) was 3.9% with a HR for death 1.9 times that of non-injured. The excessive mortality in study II was almost confined to patients with a delayed discovery of the BDI due to postoperative bile leakage. The mortality figures reflect the detrimental impact of BDI but are considerably lower than those presented by Flum et. al.[2], who reported a one-year mortality of 26% after BDI in his Medicare cohort, using identical methodology to study I. However, the one-year mortality of non-injured Medicare patients was as high as 6.6% reflecting the selection of an elderly population with significant comorbidity and severe socioeconomic situation, hardly comparable to the Swedish population of study I and II. In contrast to these results, DeReuver et. al.[140] reported a 10-year survival rate after BDI comparable to the general Dutch population, analysing 500 BDI patients treated at a tertiary referral centre in Amsterdam. Although a selected group, the striking survival differences compared to the results of Flum's and the present studies, reflects the positive impact of proper multidisciplinary management by highly dedicated experts. It furthermore highlights the need of gaining acceptance for an early referral regime among the surgical community, used to taking care of their own complications.
Study I further contributes to the knowledge of morbidity associated with BDI as the long follow-up allows for analyses of late complications. Patients requiring surgical

repair after BDI had a more than 4 times elevated Standardized Mortality Ratio of death due to liver related diseases, mainly cholangitis. Although not fully understood, a damage to the delicate vascularization of the biliary tree, often difficult to detect during the initial cholecystectomy, may be part of the explanation of late stricture development. A causal chain from stricture development, due to non-optimal healing after BDI repair, to biliary stasis and recurrent cholangitis points out the necessity of giving BDI patients the best available treatment. The 500 Dutch BDI patients in DeReuver's[140] study were as previously mentioned at no excessive risk of death compared to the general population, but in 10 out of 42 deaths in the BDI group during follow-up, death was believed to be related to the biliary injury. Knowledge about morbidity and late complications emphasizes the importance of doing the right thing from start, choosing the optimal reconstruction strategy with the best timing, and having a thorough short- and long term follow-up regime in the handling of BDI.

6.2.3 Prevention of bile duct injury

Study III, IV and parts of study II are dedicated to the prevention of BDI, addressing important hypothesized risk factors and the widely debated use of IOC. Study II and III are based on the valid, Swedish Registry for Gallstone Surgery, GallRiks which offers unique conditions for high evidence research. Study IV aims for a complementary investigation of the importance of acute cholecystitis, not available for detailed evaluation in the GallRiks registry.

6.2.3.1 Risk factors

6.2.3.1.1 Age

Patients' age was an independent and significant risk factor for BDI in the risk factor analyses of study III. Age was furthermore a risk factor for death after sustaining a BDI (Study I and II). The findings are in line with result from previous research[118, 120, 122]. Although there are many risks in performing surgery in elderly, many patients do well and benefits from the surgical procedure. Age alone should never be used as a criterion to deny patients otherwise indicated surgery.

6.2.3.1.2 Gender

In none of the studies of risk factors for BDI or risk factors for mortality after BDI did gender matter significantly. This might seem surprising as male gender has been associated with both excessive BDI rates and impaired survival in the few larger population based studies published[118, 122, 153]. However, these studies suffer from potential remaining confounding, better dealt with using information-dens registries as GallRiks. This statement may be supported by the consequent pattern of male gender being a risk factor in the crude analyses, but not after multivariable adjustment. The most important confounder being acute cholecystits, twice as common as indication for surgery among men compared to women.

6.2.3.1.3 Comorbidity

The burden of comorbidity, quantified by the validated[217] Charlson comorbidity index in study I and IV and by ASA-grade in study II and III, was an independent risk factor for BDI and impaired survival in all studies. These findings are in line with previous research, probably reflecting patients with a higher rate of previous surgery and more adhesions as well as the influence of non-surgical factors on wound-healing and recovery. It might furthermore represent residual confounding of a more advanced gallbladder disease and consequently more difficult procedures.

6.2.3.1.4 Acute cholecystitis

A main finding of paper III and IV is the impact of acute cholecystitis on the risk of BDI. Acute cholecystitis is a relatively common complication to gallstone disease with laparoscopic cholecystectomy as the treatment of choice. Previous population-based studies have not been able to show the association between increased BDI-rates and acute cholecystitis, mainly due to methodological limitations. The significant findings of Study III confirm, on a population-based level, that the presences of inflammation of the gallbladder or a history of inflammation are important risk factors for BDI. Furthermore, patients with acute cholecystitis benefits from early cholecystectomy, as soon as possible after emergency admittance.

The suggested safety of laparoscopic cholecystectomy in patients with acute cholecystitis is based on high level evidence from randomized controlled trials. However, patients with acute cholecystits are a very heterogeneous group and in severe forms, often in combination with advanced age and comorbidity, cholecystectomy may result in serious morbidity and mortality[93-95, 218-220]. These patients are rarely included in randomized trials and the recommendations cannot be generalized to this patient group. In study IV, patients with acute cholecystitis were stratified according to severity and the findings are important. Patients with mild (Tokyo grade I) acute cholecystitis are at no excessive risk for sustaining BDI at cholecystectomy whereas moderate (Tokyo grade II) and severe (Tokyo grade III) forms have a gradually increasing injury risk. These findings imply the need of more research aimed for safe alternative treatments of acute cholecystitis and high risk patients.

6.2.3.1.5 Other risk factors

In the risk factor studies (study III, and IV) we investigated, but did not find any influence on BDI risk by patients BMI or the annual cholecystectomy caseload of surgeons and hospitals.
The analyses suggested an increased risk by open cholecystectomy compared to laparoscopic approach, a finding most likely the result of residual confounding by a selection of suspected difficult cases to the open technique.

CBDS were found at a higher rate among BDI compared to non-injured cholecystectomised patients. It suggests that CBDS might cause postoperative bile leakages by increasing the intraductal pressure, causing cystic stump blow-outs and persisting leaks from minor BDI. The results are however suffering from selection bias, as only patients with a successful IOC have the possibility of CBDS detection.

6.2.3.2 Intraoperative cholangiography

The controversies regarding a possible protective effect of IOC against BDI have been an on-going matter of debate since even before the introduction of laparoscopic cholecystectomy. As high level evidence from randomized controlled trials is virtually impossible due to the rareness of BDI, single or multicentre case series, questionnaire based research, and observational population based research have, without success, tried to convince the surgical community of either the pros or cons of IOC.
All of the four studies within this thesis are to some extent investigating the relationship between IOC and BDI. In study I, evaluating 374 042 cholecystectomies from 1965 to 2005, the use of IOC significantly reduced the risk of death in patients with reconstructed BDI by 27%. The widely used methodology based on ICD-codes can however be questioned and the results are somewhat ambiguous. Study II, using the prospectively collected and valid GallRiks registry, poses major advantages regarding injury and IOC identification and represents the best level of evidence available on this topic. We introduced *the intention-to-do IOC*, including failed cholangiography attempts. IOC intention significantly reduced BDI rates by 29%, facilitating early injury detection. Moreover, the intentional use of IOC reduced the risk of death after cholecystectomy by 62%.

Among the drawbacks of IOC, the prolonged operation time, added costs and risk of misinterpretation have made the selective approach dominating using IOC only in high risk patients. Available research have, up-to-date, not been able to show the safeness of this approach and the definition of high risk patients have not been clarified. In study III, we stratified the effect of intentional IOC on patients with acute cholecystitis, with a history of acute cholecystitis and with uncomplicated gallstone disease. It became evident that the protective effect of IOC on BDI risk was confined to patients with acute cholecystitis and patients with a history of acute cholecystitis. Patients with uncomplicated gallstone disease did not significantly benefit from IOC.
The results from these studies, based upon best available data, suggest that the intention of IOC reduces BDI rates and improves outcome and survival after cholecystectomy. Evidence based recommendations of a selective approach can only be made among patients with uncomplicated gallstone disease whereas in patients with gallstone complications, such as acute cholecystitis, IOC should be routinely performed.

7 CONCLUSIONS

This thesis provides results to support the following conclusions:

- The incidence of iatrogenic BDI in Sweden is approximately 1.5%, including minor and major injuries.

- Iatrogenic BDI during cholecystectomy is associated with reduced short and long-term survival.

- Patients with reconstructed BDI are at increased risk of dying from liver related diseases, especially cholangitis.

- Increasing age and comorbidity are risk factors for BDI, and affects survival negatively following a BDI.

- Patients with moderate (Tokyo grade II) or severe (Tokyo grade III) forms of acute cholecystitis or patients with a history of acute cholecystitis are at increased risk of iatrogenic BDI during cholecystectomy. On the other hand, patients with mild acute cholecystitis (Tokyo grade I) do not have an increased injury risk compared to patients without inflammatory changes of the gallbladder.

- Postoperative, as opposed to peroperative, detection of BDI increases the risk of dying after a cholecystectomy.

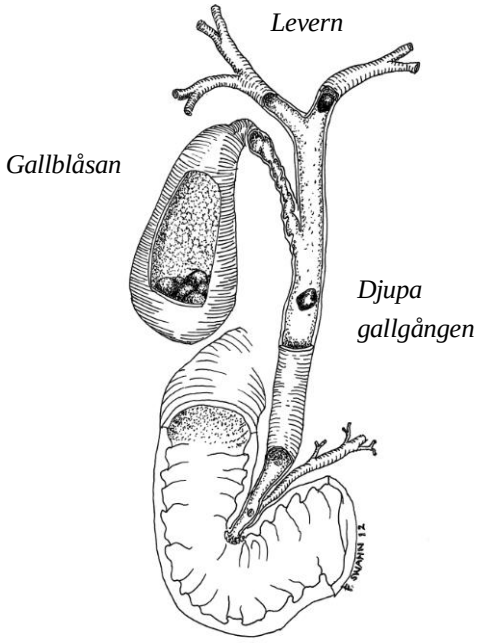
- IOC reduces iatrogenic BDI rates at cholecystectomy and improves survival after cholecystectomy.

- The protective effect of IOC is confined to patients with acute cholecystitis or patients with a history of acute cholecystitis. Patients with uncomplicated gallstone disease does not significantly benefit from IOC.

8 POPULÄRVETENSKAPLIG SAMMANFATTNING

Gallstenar har plågat mänskligheten genom historien, där den tidigaste påträffade gallstenen återfanns i den mumifierade kroppen av en Egyptisk prästinna från Amen (1085-945 f.Kr). Idag får gallstenssjukdomen betraktas som en folksjukdom, där ca var fjärde person i Sverige någon gång kommer utveckla gallsten, kvinnor i ca dubbelt så stor utsträckning som män. Även om endast en minoritet får symtom eller komplikationer av sina gallstenar kommer mellan 10 och 40 % att genomgå en operation någon gång i livet. Detta gör att en gallstensoperation, eller kolecystectomi, är den näst vanligaste operationen i Sverige med ca 11500 ingrepp varje år. En kolecystektomi är idag ett rutiningrepp, vanligen utfört med titthålskirurg, där patienten ofta går hem samma dag och återgår i arbete endast efter några dagars sjukskrivning. Allvarliga komplikationer är ovanliga men kan ge förödande konsekvenser.

Denna avhandling fokuserar på den kanske mest förödande komplikationen under en kolecystektomi, en oavsiktlig skada på gallgångarna mellan levern och tolvfingertarmen.
Lyckligtvis är skador relativt ovanliga och har rapporterats hos ca 0.5% av alla kolecystektomier. En allvarlig skada är potentiellt livshotande, innebär en lång sjukhusvistelse, ofta med behovet av flera kirurgiska ingrepp för att rekonstruera gallträdet, och samhällskostnaderna kan bli mycket stora.
Den överlägset bästa metoden att behandla gallgångskador är att förebygga dem, och för det krävs en djup förståelse avseende uppkomst, konsekvenser, riskfaktorer och kirurgisk teknik. Tidigare forskningsinsatser inom detta område har haft svårigheter att kunna presentera tillförlitliga resultat som är säkra nog att bygga rekommendationer och behandlingsriktlinjer utifrån. I synnerhet har användande av gallvägsröntgen, s.k. intraoperativ kolangiografi, varit synnerligen omdebatterat. Förespråkare hävdar att denna röntgen minskar risken för skador medan motståndarna lyfter fram en förlängd operationstid, ökade kostnader och tveksam effekt.



Figur10. *Gallblåsan och gallvägarna.* © Fredrik Swahn, 2012

Genom fyra delarbeten har det i denna avhandling undersökts hur vanligt gallgångskador är, vilka konsekvenser det får för patienten avseende sjuklighet och överlevnad, vilka riskfaktorer det finns samt hur effektivt skador kan förebyggas med optimalt använda kirurgiska metoder.

I det första delarbetet användes slutenvårdsregistret där data från alla behandlingar på svenska sjukhus registrerats från 1965. Data från åren 1965-2005 analyserades. 374 042

kolecystektomier och 1386 gallgångskador som genomgått kirurgisk rekonstruktion återfanns. Överlevnaden hos denna grupp var betydligt sämre än hos patienter utan skador och ca 10% dog inom det första året. Leverrelaterade sjukdomar var överrepresenterade som dödsorsak i denna grupp vilket talar för att skadan medför svårigheter för gallan att flöda fritt ut till tarmen med stas upp i levern som följd.

I det andra delarbetet användes det svenska kvalitetregistret för gallstenskirurgi, GallRiks, som startades på uppdrag av Svensk Kirurgisk Förening 2005. Registret har snabbt kommit att bli ett av världens mest kompletta register över gallstensbehandlingar och täcker idag mer än 90% av alla kolecystektomier i Sverige. Genom att analysera 51 041 kolecystectomier mellan 2005 och 2010 fann vi 747 (1.46%) gallgångskador, från små skador med endast läckage av galla till skador där stora delar av gallträdet oavsiktligt opererats bort. Överlevnaden efter en gallgångskada var bättre om skadan upptäcktes i samband med den ursprungliga operationen istället för efteråt. Ett viktigt fynd var även att gallgångsröntgen visade sig förbättra överlevnaden efter kolecystektomi, troligen p.g.a. att skador upptäcks i ett tidigt skede och begränsas i sin omfattning.

I det tredje delarbetet fortsatte analyserna av materialet från GallRiks med speciellt intresse på riskfaktorer för gallgångskada och effekten av gallvägsröntgen. Resultaten visade att hög ålder, övrig sjuklighet och en pågående inflammation i gallblåsan vilket är en relativt vanlig orsak till operation, ökar risken för gallgångskada. Även patienter med en tidigare akut inflammation i gallblåsan, men ingen pågående vid operationstillfället, har en ökad skaderisk. Ett mycket viktigt fynd var att den skyddande effekten av gallvägsröntgen var som mest uttalad hos patienter med just pågående inflammation i gallblåsan. Skaderisken halveras hos denna grupp om röntgen används. Patienter med okomplicerade gallstensbesvär, utan inflammation har däremot ingen skyddande effekt av röntgen.

I det fjärde och sista delarbetet fördjupades studierna av akut inflammation i gallblåsan och dess inverkan på skaderisk. Genom en s.k. fall-kontrollstudie, med journalgenomgång av 158 gallgångskador och 623 oskadade gallstensopererade kontrollpatienter, undersöktes om patienter med olika grader av inflammation har olika risk att drabbas av gallgångskada. Resultaten visar att patienter med mild inflammation inte har någon ökad risk medan patienter med måttlig eller svår inflammation har en gradvis ökad risk. Detta talar för att man kan behöva anpassa behandlingen och kanske till och med undvika operation när inflammationen är riktigt uttalad.

Sammanfattningsvis har denna avhandling kunnat visa att gallgångskada vid kolecystektomi är vanligare än man tidigare trott, med försämrad överlevnad som följd. Detta beror sannolikt på en ökad dödlighet i leverrelaterad sjukdom orsakad av gallgångskadan. Hög ålder, samtidiga sjukdomar och inflammatoriska förändringar i gallblåsan är viktiga riskfaktorer för gallgångskada. Rätt användande av gallvägsröntgen minskar skaderisken och förbättrar överlevnaden efter kolecystektomi. Då den skyddande effekten av gallvägsröntgen kan visas hos patienter med inflammatoriska förändringar i gallblåsan bör detta utföras rutinmässigt hos denna patientkategori. Hos patienter med okomplicerade gallstensbesvär kan ett selektivt användande vara lika säkert.

9 ACKNOWLEDGEMENTS

This thesis, and the four papers within, would not have been possible without the support and encouragement of many people. I would like to express my sincere gratitude to the following persons:

Magnus Nilsson, Associate professor, Head of the Department of Upper Abdominal Surgery, main supervisor and friend. For your support, genuine faith in me and dedication to this project. Your professional and personal abilities go beyond comparison.

Jörgen Larsson, Professor of Surgery, Head of the Division of Surgery, CLINTEC and assistant supervisor. For your generous support throughout this PhD program and during my professional career. Thank you for hiring me eight years ago, despite my interest in golf...

Weimin Ye, Professor of Epidemiology, MEB and assistant supervisor. For your contributions of statistical expertise and advice.

Lars Enochsson, Associate Professor, co-author of Paper III. For your commitment to registry based research, and for providing me with time to finish this thesis.

Anne Waage, senior consultant surgeon, co-author of Paper II and IV. For relieving me of a significant number of dusty medical records in communities of mid-eastern Sweden.

Cecilia Strömberg, senior consultant surgeon, co-author of Paper II and III. For your company during many research courses, sharing moments of frustration trying to master medical biostatistics.

Zongli Zheng, MD, PhD, co-author of Paper I and IV. For important help and statistical guidance.

Olof Akre, Associate Professor, co-author of paper III. For important epidemiological input and advice.

Gunnar Persson, MD, PhD, co-author of Paper II. For providing GallRiks data.

Rozh Noel, MD, for contributing to the gathering of medical records to paper IV. Good luck with your own thesis project!

Steven Strasberg, Professor of Surgery, University of Washington St. Louis. For important feed-back and research input during your visit to Karolinska in 2012.

Hélène Jansson, secretary at the Division of Surgery, CLINTEC. For administrative guidance and support, and for helping me with the layout of this book.

Johan Permert, Professor of Surgery and **Claes Jönsson**, Associate Professor, former and present Chairman of the Surgical Department. For providing the conditions necessary for academic research.

Åke Andrén-Sandberg, **Lars Lundell** and **Matthias Löhr**, Professors of Surgery. For your efforts to obtain the highest scientific standards at our department, and for contributing with your impressive national and international networks.

Urban Arnelo, senior consultant surgeon and **Fredrik Swahn**, consultant surgeon, members of the Endoluminal surgery team. For teaching me the techniques and beauty of advanced endoscopic surgery.

Eduard Jonas, senior consultant surgeon. For mentoring me and sharing the devotedness of spending hours removing tiny, tiny pieces of neoplastic mucosa…

Mari Hult, consultant surgeon, desk neighbour. For you good spirits and for constantly keeping me informed about everything.

Christel Nilsson, secretary of the Division of Upper Abdominal Surgery. For your kind assistance and devotedness to the stressed surgeons of this department.

All of my skilled and devoted colleagues at the Department of Surgical Gastro-enterology, Karolinska University Hospital. In particular my co-workers at the Department of Upper Abdominal Surgery Drs. (in alphabetic order) **Thorhallur Agustsson, Christoph Ansorge, John Blomberg, Marco del Chiaro, Melroy D'Souza, Peter Elbe, Stefan Gilg, Bengt Isaksson, Anders Jansson, Ann Kjellin, Koshi Kumagai, Mats Lindbladh, Per Lundquist, Afshin Noorani, Madelene Olsson, Elena Rangelova, Ioannis Rouvelas, Ralf Segersvärd, Ernesto Sparrelid, Jon Tsai, Mikael Wirén** and **Cecilia Wredberg.**

Staffan Roos, PhD, good old friend, soulmate. For the agony caused by the proofreading this book and for the past and future sharing of many recovering glasses of single Malt by the fire in "Boddan".

My beloved sister **Annika** and brother in law **Niclas**, for always being there. You have made this book possible...

My beloved brother and sister **Henrik** and **Catharina**, for your love and concern of our family.

My beloved father **Anders**, for inspiring med to become a doctor. For your and **Cisa**'s never ending love and support to me and my family.

My beloved mother **Sonja**, for your unconditional love and making me who I am.

My wife **Annelie** and daughters **Linnéa** and **Olivia**. For being everything.

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