Outcome Analysis for Laparoscopic and Open Cholecystectomy

SATU SUURONEN

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ABSTRACT

Gallstone disease is common in developed countries, and cholecystectomy is one of the most frequently performed abdominal operations. More advanced age, obesity, and diabetes are known risk factors for gallstone formation. The increased prevalence of these risk factors among the Finnish population is likely to increase the prevalence of symptomatic gallstone disease and subsequent need for surgical management. Over the last two decades, laparoscopic cholecystectomy (LC) has become the gold standard in the treatment of symptomatic gallbladder disease – it is associated with lower morbidity and mortality than arise with the traditional approach of open cholecystectomy (OC),

The aim of the study was to assess the outcomes of laparoscopic and open cholecystectomy at one Finnish non-university teaching hospital and in Finnish registry-based data, via analysis of 1) the outcomes of LC and OC operations performed by surgical residents, with special emphasis on the occurrence of bile duct injuries; 2) the outcomes of LC and OC procedures in diabetic patients; 3) the impact of obesity, ageing, diabetes, and statin use on the rate of cholecystectomies in a Finnish population-based cohort and in a community-based hospital cohort; and 4) the incidence of bleeding complications and transfusions associated with LC and OC in a Finnish register-based cohort. Data were collected for all cholecystectomies performed for benign gallbladder disease at the study hospital in 1995–2008. To enable assessment of bleeding complications and transfusion rates, data pertaining to LC and OC operations and related blood-component use between 2002 and 2007 were collected from the Optimal Use of Blood (or 'Verituotteiden optimaalinen käyttö', VOK) registry.

The results show that, firstly, with careful patient selection, LC performed independently by surgical residents is safe. Secondly, LC is a safe procedure in diabetic patients with symptomatic gallstone disease. Although the rate of conversion to open surgery was elevated among diabetic patients, the complication rate was lower than or comparable to that in primary open cholecystectomy. Thirdly, the LC rate increased in Finland between 1995 and 2008, but the total rate of cholecystectomies remained stable or decreased slightly, although the prevalence of risk factors for gallstone disease rose in the population. The impact of the substantial increase in statin use on the incidence of symptomatic gallstone disease warrants further study. Fourthly, LC is associated with lower rates of transfusion of blood components than OC is. The similarity observed between LC and OC in per-transfusion-patient mean transfused doses and the mean costs of transfused blood components indicates that the severity of bleeding complications may not differ substantially between OC and LC.

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Medical Subject Headings: Cholecystectomy; Cholecystectomy, Laparoscopic; Cholelithiasis; Bile Ducts/injuries; Conversion to Open Surgery; Postoperative Complications; General Surgery/education

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TIIVISTELMÄ

Sappikivitauti on yleinen kehittyneissä maissa ja sappirakon poisto on yleisimpiä vatsaelinkirurgisia toimenpiteitä. Ikääntyminen, lihavuus ja diabetes ovat sappikivitaudin tunnettuja riskitekijöitä. Näiden riskitekijöiden yleistyminen suomalaisessa väestössä voi johtaa oireisen sappikivitaudin lisääntymiseen ja siten lisätä kirurgisen hoidon tarvetta. Kahden viimeisen vuosikymmenen aikana laparoskooppisesta sappirakon poistosta on tullut oireisen sappikivataudin hoidon kultainen standardi. Laparoskooppisiin sappirakon poistoihin liittyy vähemmän komplikaatioita ja kuolleisuutta kuin avoimiin sappirakon poistoihin.

Tutkimuksen tarkoituksena oli selvittää laparoskooppisten ja avoimien sappirakon poistojen tuloksia suomalaisessa keskussairaala-aineistossa ja suomalaisessa rekisteriaineistossa. Tutkimuksessa analysoitiin 1) erikoistuvien lääkärien suorittamien laparoskooppisten ja avoimien sappirakon poistojen tuloksia erityisenä kiinnostuksen kohteena sappitievaurioiden esiintyvyys 2) laparoskooppisten ja avoimien sappirakon poistojen tuloksia diabeetikoilla 3) lihavuuden, ikääntymisen, diabeteksen ja statiinien käytön vaikutuksia sappirakon poistojen määrään suomalaisessa väestökohortissa ja keskussairaala-aineistossa 4) sappirakon poistoihin liittyvien vuotokomplikaatioiden ja verensiirtojen esiintyvyyttä suomalaisessa rekisteriaineistossa. Tutkimusta varten kerättiin tiedot kaikista vuosina 1995–2008 tutkimussairaalassa sappikivitaudin takia tehdyistä sappirakon poistoista. Vuotokomplikaatioden ja verensiirtojen tutkimiseksi kerättiin laparoskooppiset ja avoimet sappirakon poistot sekä niihin liittynyt verituotteiden käyttö vuosilta 2002-2007 VOK-rekisteristä (Verituotteiden optimaalinen käyttö).

Tutkimuksessa todettiin, että laparoskoopinen sappirakon poisto on turvallinen toimenpide erikoistuvan lääkärin suorittamana, kun potilaat valitaan huolellisesti. Toiseksi laparoskooppinen sappirakon poisto on turvallinen toimenpide oireisesta sappikivitaudista kärsivillä diabeetikoilla. Vaikka konversiot eli tähystysleikkauksen muuttamiset avoleikkaukseksi olivat yleisempiä diabeetikoilla, oli komplikaatioiden esiintyvyys matalampi tai samankaltainen kuin primääreissä avoleikkauksissa. Kolmanneksi laparoskooppisten sappirakon poistojen määrä kasvoi Suomessa 1995–2008, mutta sappirakon poistojen kokonaismäärä pysyi samana tai väheni hieman, vaikka sappikivitaudin riskitekijät yleistyivät väestössä. Statiinien käytön huomattavan lisääntymisen vaikutus oireisen sappikivitaudin esiintyvyyteen vaatii lisätutkimuksia. Neljänneksi laparoskooppisiin sappirakon poistoihin liittyy vähemmän verituotteiden käyttöä kuin avoimiin sappirakon poistoihin. Havaitut samankaltaiset siirrettyjen verituotteiden keskimääräiset annokset ja siirettyjen verituotteiden keskimääräiset kustannukset siirron saanutta potilasta kohti viittaavat siihen, ettei vuotokomplikaatioiden vakavuudella ei ole merkittävää eroa laparoskooppisissa ja avoimissa sappirakon poistoissa.

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Satu Suuronen
Lauttasaari, February 2016

List of original publications

This dissertation is based on the following original publications, which will be referred to in the body of the text by their Roman numerals, I–IV. Additionally, some previously unpublished data are presented.

I Suuronen S, Koski A, Nordstrom P, Miettinen P, and Paajanen H. Laparoscopic and open cholecystectomy in surgical training. *Digest Surg. 2010;27:384–90*.

II Paajanen H, Suuronen S, Nordstrom P, Miettinen P, and Niskanen L. Laparoscopic versus open cholecystectomy in diabetic patients and postoperative outcome. *Surg Endosc. 2011;25:764–70*.

III Suuronen S, Niskanen L, Paajanen P, and Paajanen H. Declining cholecystectomy rate during the era of statin use in Finland: a population-based cohort study between 1995 and 2009. *Scand J Surg. 2013;102:158–63*.

IV Suuronen S, Kivivuori A, Tuimala J, and Paajanen, H. Bleeding complications in cholecystectomy: a register study of over 22,000 cholecystectomies in Finland. *BMC Surg. 2015;15:97*.

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Abbreviations

ASA	American Society of Anesthesiologists
BDI	Bile duct injury
BMI	Body mass index
CBD	Common bile duct
CBDE	Common bile duct exploration
CBDS	Common bile duct stones
ERCP	Endoscopic retrograde cholangiopancreatography
EUS	Endoscopic ultrasonography
FFP	Fresh frozen plasma
HDL	High-density lipoprotein
IOC	Intraoperative cholangiography
LC	Laparoscopic cholecystectomy
LERV	Laparoendoscopic rendezvous
MRCP	Magnetic resonance cholangiopancreatography
OC	Open cholecystectomy
PLTs	Platelets
RBCs	Red blood cells
RHA	Right hepatic artery
RHAI	Right hepatic artery injury
US	Ultrasonography
SO	Sphincter of Oddi

1 Introduction

Gallstone disease is commonplace in the developed countries, with a prevalence of 10–15% (1). The prevalence increases with advancing age, and female gender is associated with a higher prevalence (2,3). Higher age, metabolic syndrome, obesity, and diabetes mellitus are all known risk factors for gallstone formation (4). As in other developed countries, the general population is ageing in Finland, where obesity, together with closely associated type 2 diabetes, also has been on the rise (5). These trends are likely to increase the prevalence of symptomatic gallstone disease and the ensuing need for surgical management at the population level.

Cholecystectomy is one of the most commonly performed abdominal operations in the developed world. Over the last two decades, laparoscopic cholecystectomy (LC) has become the gold standard in the treatment of symptomatic gallbladder disease: in comparison to the traditional approach, open cholecystectomy (OC), LC is associated with lower morbidity (6,7) and mortality (7,8) rates, shorter hospital stays (9), and more rapid return to the patient's normal activities (10). However, LC is associated with slightly higher incidence of iatrogenic bile duct injury (BDI) than was reported for OC in the pre-laparoscopic era (11–13).

The literature has focused on biliary complications of LC, yet major vascular complications, though rare, are the most serious complications of laparoscopy (14,15). Major bleeding in cholecystectomy is associated with significant morbidity and mortality (11,16). In addition, bleeding remains a frequent cause of conversion (17–20).

Nowadays, according to register-based studies, as many as 90% of all cholecystectomies are performed via laparoscopic technique (7,8,21,22). The open procedure is still performed particularly often for elderly patients (7,21) and in cases of acute cholecystitis (8,23). In addition, this technique is needed when the laparoscopic operation cannot be completed safely and conversion to an open procedure is required. According to the literature, conversion rates vary between five and 10 per cent (19,20,24,25).

The declining number of OC operations means that surgeons' experience with the open technique is growing more and more limited. This development affects surgical training especially, given that surgical residents should still be adequately trained to complete a cholecystectomy employing an open technique.

This thesis was designed to assess the outcomes of laparoscopic and open cholecystectomy at the case Finnish non-university teaching hospital. Special emphasis was placed on diabetic patients, bleeding complications, BDI, and surgical training in laparoscopic cholecystectomy.

2 *Review of the Literature*

2.1 ANATOMY AND PHYSIOLOGY OF THE BILIARY TRACT

The development of the biliary tract begins in the fourth week of gestation, when the liver bud arises from the foregut (26). The precursor to the bile duct is formed between the developing liver parenchyma and foregut (26). The gallbladder primordium buds off the caudal portion of the bile duct, giving rise to the gallbladder and cystic duct between the fourth and fifth week of gestation. The extrahepatic biliary tree develops in close concert with the hepatic artery (27), but the details of this development remain nebulous (28).

The embryonic development of the biliary tract is highly complex, and the anatomy involved exhibits a wide range of variation. The typical gross anatomy of the biliary tract is shown in Figure 1. Usually, left and right hepatic ducts exit the liver and join to form the common hepatic duct. The length of the cystic duct varies, and it usually joins the common hepatic duct to form the common bile duct (CBD) (29). The length of the CBD varies within the 7–11 cm range (28), with the normal diameter falling within the range 4–10 mm (30). The CBD drains to the duodenum and, classically, it joins with the main pancreatic duct to form the papilla of Vater (31).

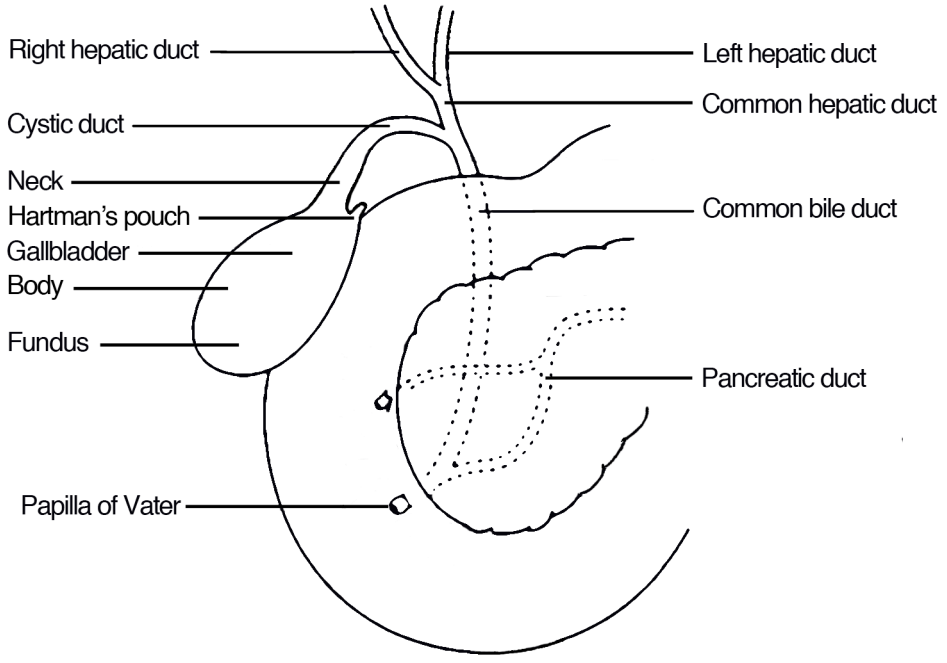

Figure 1. Anatomy of the extrahepatic biliary tract.

Bile flowing from the liver drains to the CBD. The resting tone in the sphincter of Oddi, at the distal end of the CBD, prevents the flow of bile into the duodenum (28,32). It also allows the bile to fill the CBD, with subsequent retrograde filling of the cystic duct and gallbladder. The gallbladder is a muscular sac behind the liver that has a capacity of approximately 30 ml. There are four parts to the gallbladder: the fundus, body, Hartmann's pouch, and neck (28). The neck drains into the cystic duct.

Approximately half of patients present with the typical biliary anatomy (33). In most cases, the right and left hepatic ducts run a short course outside the liver parenchyma before uniting to form the common hepatic duct (34). Rarely, the right and left ducts join within the liver. Alternatively, they may run separately and join lower, at the level of the

drainage site of the cystic duct. Anatomical variations in the first-order branching of the right and left hepatic ducts within the liver are common. Atypical branching patterns of the right hepatic duct are present in approximately 14% of patients and atypical branching patterns of the left hepatic duct in 8% (33,35).

The anatomy of the cystic duct presents a wide range of variation, and it is estimated that only a third of the population have the typical cystic duct anatomy (36). Low cystic duct insertion within the distal third of the CBD is present in 8–14%. Rarely, the cystic duct opens into the right hepatic duct (37–39). The union of the cystic duct with the common hepatic duct is characterised as angular (75%), parallel (20%), or spiral (5%) (36,40).

As does the rest of the biliary tract, the papilla of Vater has variable anatomy. The bile duct and pancreatic duct typically join to form a well-defined papilla with a common channel. This is seen in 60% of cases. Most other patients have ducts that remain separate through the wall of the duodenum but share an opening at the papilla, the so-called double barrel. On rare occasions, the ducts empty into the duodenum separately (41,42).

The main arteries supplying the CBD originate from the gastroduodenal and right hepatic artery (43). About 60–70% of patients display the classic hepatic arterial anatomy, wherein the hepatic artery bifurcates to form the right and left hepatic artery (44,45). The right hepatic artery (RHA) usually runs posterior to the CBD. In 22% of cases, it is anterior to the CBD (46). Up to 20% of patients have an aberrant right hepatic artery, most commonly arising from the superior mesenteric artery (44,45,47). These vessels typically take a course posterior to the portal vein and the CBD. The blood supply to the gallbladder comes from the cystic artery, a branch of the right hepatic artery (43).

Venous drainage of the gallbladder includes veins that follow along the cystic and hepatic ducts to drain into the liver via the portal system as well as veins that drain directly into the liver (28,48,49).The lymphatic vessels of the gallbladder drain to the gallbladder's sentinel lymph node (sometimes referred to as Calot's node) and lymph nodes along the porta hepatis. Lymphatic drainage can also flow directly into the liver before reaching lymph nodes within the hepatoduodenal ligament (50,51). The parasympathetic innervation of the biliary tract comes from the vagus nerve, and the sympathetic innervation from the celiac plexus. Parasympathetic innervation promotes contraction of the gallbladder, whereas sympathetic stimulus promotes relaxation of the gallbladder smooth muscle tissue (52,53). Similarly to the rest of the intestinal tract, the gallbladder is innervated by the enteric nervous system, participating in the co-ordination of muscle function (28,54,55).

Bile is a lipid-rich hepatic secretion that is necessary for elimination of cholesterol and xenobiotics from the body, along with intestinal digestion and efficient absorption of nutrients. The liver produces 600–750 ml of bile daily (4). It is secreted primarily by hepatocytes and subsequently delivered to the intrahepatic bile ducts, where it is modified by cholangiocytes. The main components of bile are bile acids (67%), phospholipids (22%), proteins (4.5%), cholesterol (4%), and bilirubin (0.3%) (56). The bile acids are the end metabolic product of cholesterol and one of the most important routes of its elimination. The size of the bile acid pool is kept relatively constant by two mechanisms: enterohepatic circulation and *de novo* synthesis (57,58). Via the former mechanism, about 95% of bile acids are absorbed in the terminal ileum (56,58).

The bile formed outside periods of digestion enters the gallbladder. The gallbladder has two important functions: concentration of bile and its storage until the time of evacuation into the duodenum (56). The flow of bile is at its lowest during fasting, when most of the bile is diverted into the gallbladder for concentration. When an ingested meal enters the small intestine, acid and partially digested fats and proteins stimulate secretion of cholecystokinin and secretin. The action of the peptide hormone secretin expands the volume of bile and increases its flow into the intestine (56). Cholecystokinin stimulates contractions of the gallbladder and common bile duct, thereby resulting in delivery of bile to the duodenum (56,59).

2.2 GALLSTONE DISEASE

The prevalence of gallstones varies with ethnic group and geographical location. The lowest prevalence, approximately 5%, is found in Asia and Africa (60–62). In the developed countries, gallstones are commonplace, with a prevalence as high as 10–15% of the adult population (1,63). The highest prevalence is found among North American Indians, in whom they afflict 64% of women and 30% of men (64,65).

2.2.1 Formation of Gallstones

There are two main types of gallstones: cholesterol stones and pigment stones. Cholesterol stones form when there is supersaturation of bile with cholesterol (66). In the supersaturated bile, cholesterol and phospholipids start to form cholesterol-rich vesicles, which make the bile lithogenic. Crystal nucleation takes place in lithogenic bile when cholesterol-rich vesicles precipitate into crystals (67,68). The crystallisation is accelerated by several pronucleating factors, including mucin glycoproteins, immunoglobulins, and transferrin (69). Formation of stones is further encouraged by decreased gallbladder motility (4,70). In the developed countries, roughly 80% of all gallstones are cholesterol stones (1,4,71).

Pigment stones account for most of the remaining 20% of gallstones in developed countries (1,4). There are brown pigment stones and black pigment stones. Black pigment stones consist of 70% calcium bilirubinate and are associated with haemolytic conditions and chronic liver disease (4,72). Brown pigment stones form as a result of stasis and infection within the biliary tract. Unlike cholesterol stones, brown pigment stones are identified mostly as primary ductal stones forming within the intrahepatic and extrahepatic bile ducts.

2.2.2 Risk Factors

The known risk factors for gallstone disease include female gender, higher age, obesity, metabolic syndrome, rapid weight loss, and diabetes; see Table 1 for a summary (4,73–75). On the basis of twin studies, it is believed that genetic factors account for 25–30% of gallstones (76,77), while the common environmental factors may account for 10–15% of gallstones and unique environmental factors for 60% (76). These studies demonstrate that even though genetic predisposition is a major risk factor and family members share environmental factors such as childhood diet, unique environmental factors, among them life-long dietary habits and physical activity, account for the largest proportion of gallstone formation.

Diets high in refined carbohydrates, high in fat, and low in fibre are associated with increased risk of gallstone formation (78–82). Physical inactivity too is associated with greater risk of gallstone disease (83). Total parenteral nutrition is a known risk factor for the development of sludge and gallstones (84). This strong correlation may be due to gallbladder stasis caused by the loss of enteric stimulation of gallbladder contraction (4).

Hypothyroidism is associated with an increased risk of gallstone formation (85). Altered cholesterol metabolism in hypothyroidism may lead to supersaturated bile (86). Additionally, hypothyroidism seems to result in reduced bile flow on account of deficiency in the prorelaxing effect of thyroxine on SO (sphincter of Oddi), thereby increasing the risk of common bile duct stones (CBDS) (87,88).

Inflammatory bowel diseases and bowel resection seem correlated with increased risk of gallstone formation (89). Impaired enterohepatic circulation of bile acid has been posited as a cause (58,90). Additionally, the conditions that result in decreased gallbladder motility, such as biliary dyskinesia or sequelae to vagotomy, are associated with an increased risk of gallstones (91,92).

Table 1. Risk factors for gallstone disease.

Risk factors for gallstone disease
Higher age
Female gender
Pregnancy/parity
Diabetes
Obesity
Metabolic syndrome
Dyslipidaemia
Rapid weight loss
Diets that are high in refined carbohydrates, high in fat, and low in fibre
Total parenteral nutrition
Physical inactivity
Decreased motility of the gallbladder
Hypothyroidism
Impaired enterohepatic circulation of bile acids

2.2.2.1 Gender and Age

Females have twice the risk of gallstone disease that men do (3,63). This greater risk is related to female sex hormones, birth-control medicines, parity, and hormone replacement therapy (93–96). In addition, pregnant women are more likely than others to suffer from symptomatic gallstones. The increased levels of oestrogen and progesterone lead to cholesterol hypersecretion and gallbladder stasis (97,98). Consequently, during pregnancy up to 30% of women develop biliary sludge and 2% develop gallstones (99).

The risk of gallstone disease increases markedly with age. After the age of 40, the incidence of gallstone disease increases by 1–3% per year (4). The contributing factors include increased hepatic cholesterol secretion, higher cholesterol saturation, and reduced bile acid synthesis (100).

2.2.2.2 Obesity and Dyslipidaemia

Obesity is a strong risk factor for gallstone disease. This may be partially due to the increased activity of 3-hydroxy-3-methylglutaryl–coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in cholesterol synthesis, leading to increased cholesterol synthesis in the liver and secretion into the bile (101). Though obese individuals hypersecrete bile salts and phospholipids in addition to cholesterol, the rate of cholesterol's hypersecretion exceeds that of bile salts' and phospholipids'. This leads to supersaturation of the bile with cholesterol and increased lithogenicity (4,102).

Abdominal adiposity has been identified as a major risk factor for gallstone disease, especially in women (103). Waist circumference and waist-to-hip ratio have been shown to be better predictors of gallstone development than either body mass index (BMI) or overall total body fat is (104).

Paradoxically, rapid weight loss increases the risk of gallstone formation. Weight reduction leads to mobilisation of hepatic stores of cholesterol (73). In combination with this, decreased gallbladder emptying and reduced bile acid synthesis lead to supersaturation of bile and to stone formation (105). After bariatric surgery, 30–70% of the patients develop gallstones (106–108).

Gallstone formation is a metabolic issue that is associated with dyslipidaemias. Hypertriglyceridaemia and low high-density lipoprotein (HDL) concentration are associated with increased risk of cholesterol stone formation (109,110). This is believed to be caused by cholesterol saturation of bile associated with these dyslipidaemias (111). However, in a study, the lipid composition of bile did not differ significantly between hypertriglyceridaemia patients and controls, but decreased sensitivity of the gallbladder to cholecystokinin was observed in hypertriglyceridaemia patients (112). Although obesity is common among dyslipidaemia patients, both hypertriglyceridaemia and low HDL have

been shown to be independent risk factors for gallstone disease (109,110). Treating hypertriglyceridaemia with fibrates increases the secretion of cholesterol into bile, thereby increasing the risk of gallstone formation (112).

2.2.2.3 Diabetes Mellitus

The prevalence of gallstone disease is higher in diabetic patients than that observed in the general population. Independent risk factors for gallstone formation in diabetics include higher age, higher BMI, and a positive family history (113). However, the association of diabetes with gallstone disease is not fully delineated. The association may be due in part to the observed alterations in bile acid composition and the size of the pool in patients with type 1 and type 2 diabetes (114,115).

Obesity, type 2 diabetes, and hypertriglyceridaemia are all associated with metabolic syndrome, which is a known risk factor for gallstone disease (116). The number of components of metabolic syndrome seems to correlate with the likelihood of gallstone disease (117).

2.2.2.4 Statin Use and Risk of Gallstone Disease

Hypercholesterolaemia is not strongly associated with gallstone disease (4,118,119). On the other hand, increased serum cholesterol levels and altered cholesterol metabolism appear to play a major role in the increased risk of gallstones associated with hypothyroidism (85,86). Nevertheless, statins, used in patients with dyslipidaemia, inhibit HMG-CoA reductase and so decrease cholesterol synthesis in the liver. Thus, statins seemingly protect against gallstone formation by decreasing the amount of cholesterol in the bile. According to a recent meta-analysis, both current and long-term use of statins seem to decrease the risk of gallstone formation relative to non-use (120). The reduction in risk via statin use may be as great as 30% (121). Yet further studies are needed to confirm these findings.

2.2.3 Symptoms

Gallstone disease can be divided into asymptomatic gallstones, symptomatic gallstones, and complications of gallstones. During follow-up, most gallstones remain asymptomatic. The risk of progression to symptomatic disease is 2–4% per year (122–124). Within five years of diagnosis, 10% of patients with gallstone disease become symptomatic, with the figure increasing to 20% at 20 years (125).

The most typical symptom of gallstone disease is biliary colic. The pain usually starts in the epigastrium or upper right quadrant and may radiate to the back. Belying its name, the pain often does not fluctuate but lasts 15 minutes to 24 hours (126). Nausea or vomiting may accompany the pain. Most patients with gallstone disease become symptomatic before any complications develop. Within one year from the first biliary colic, the symptoms recur in 50% of patients and 1–2% of patients develop a complication (72,125).

Biliary colic is at one end of the spectrum in symptomatic gallstone disease. Approximately 10–20% of patients with biliary colic eventually develop cholecystitis, the most common complication of gallstone disease (4,127). Acute cholecystitis is defined as inflammation of the gallbladder. It is generally caused by obstruction of the cystic duct. When the cystic duct is obstructed, most commonly by gallstones, the gallbladder mucosa continues to produce mucus though there is no outlet for drainage. This situation leads to increased gallbladder pressure and venous stasis, followed by arterial stasis and gallbladder ischaemia and necrosis (128). At the other end of the spectrum is cholangitis. Bile is normally sterile, but if an obstructed common bile duct becomes contaminated with bacteria, usually via reflux from the duodenum, cholangitis may develop. Other gallstone complications include CBDS with jaundice, gallstone pancreatitis, and gallstone ileus (72,129–131).

Gallstone disease is a known risk factor for gallbladder carcinoma. One possible explanation is that the presence of gallstones creates chronic inflammation of the mucosa, which leads to dysplasia over time. The risk of a patient with asymptomatic gallstones developing cancer is 0.01% (72,132), which is less than the mortality rate associated with cholecystectomy (7,8,22,24). Therefore, prophylactic cholecystectomy is not indicated in order to prevent future gallbladder cancer in the general population with asymptomatic gallstone (133–135). Nevertheless, there is a greater risk of gallbladder carcinoma associated with stones larger than 3 cm, the risk being 4% over 20 years (4,136,137).

2.2.4 Diagnosis and Treatment

Transabdominal ultrasonography (US) is the gold standard for diagnosis of gallbladder stones. Approximately 95% of gallbladder stones can be detected by modern US (138,139). About 10% of those patients with gallbladder stones have concomitant CBDS (72,140–142). In cases of a dilated biliary tree being found in US or of abnormal liver function tests, CBDS should be suspected.

Patients at low risk of CBDS do not require further examinations before (laparoscopic) cholecystectomy (143). The treatment of gallbladder stones is discussed in detail in Section 2.3.

For suspected CBDS, there are two common approaches to diagnosis and management. The 'laparoscopy-first' approach relies on intraoperative cholangiography (IOC) for diagnosis and laparoscopic common bile duct exploration (CBDE) for treatment. On the other hand, the 'endoscopy-first' approach refers to various techniques, such as magnetic resonance cholangiopancreatography (MRCP), endoscopic ultrasonography (EUS), and endoscopic cholangiopancreatography (ERCP), for diagnosis and entails ERCP and related endoscopic techniques (namely, endoscopic sphincterotomy and lithotripsy) for treatment (143).

With respect to CBDS diagnosis, IOC, EUS, and MRCP are reported to have similar results and very low morbidity (143–147). On account of recent advances in computed tomography (CT), the results of CT cholangiography in detecting CBDS are comparable to those of MRCP (148). In addition to the exposure to x-rays, CT cholangiography has been traditionally considered inferior to MRCP on account of accuracy issues, and it is not widely used at present. In turn, ERCP has been progressively abandoned as a diagnostic tool for CBDS because of the morbidity and mortality associated with it. The associated rate of acute pancreatitis is 2–11% (143). The EUS approach involves endoscopy under sedation so is intrinsically more invasive than MRCP. However, it may avoid the ERCP-related morbidity, with virtually no associated post-procedure acute pancreatitis (143,149–151), while still offering potential for an endoscopic therapeutic option during the same session. The invasive nature of EUS and the need for special instrumentation and expertise render it feasible only when the risk of having CBDS is high enough to allow patients the potential of taking advantage of the therapeutic endoscopy option (150,151).

Most CBDS is due to gallstone migration from the gallbladder, which creates a formal indication for cholecystectomy in most cases (124). In elderly patients, however, expectant management may be a feasible option after treatment of CBDS (152). A recent meta-analysis did not find any significant differences in overall mortality and morbidity, which ranged from 0% to 3% and 13% to 20%, respectively, when results were compared in randomised trials between management of gallbladder and CBD stones by open surgery, laparoscopic surgery, and various laparoscopic-endoscopic protocols (153). However, in terms of retained CBD stones, surgical management was superior to endoscopic management. Additionally, laparoscopic one-stage management seems to be associated with a shorter hospital stay and lower total costs than two-stage laparoscopic-endoscopic protocols are (143). Yet cost-effective laparoscopic CBDE remains both time-consuming and technically demanding, and it requires dedicated instruments. In addition, consensus has not been

reached on CBDS management, and endoscopic treatment remains largely preferred worldwide (143).

Additionally, laparoendoscopic rendezvous (LERV) has been proposed as an alternative single-stage approach (154). It facilitates the endoscopic procedure during LC by the insertion of a guide wire through the cystic duct and CBD into the duodenum, avoiding inadvertent cannulation of the pancreatic duct (154). Another element contributing to the safety and effectiveness of the procedure is the injection of the contrast medium by the surgeon through the cystic duct; there is no direct injection into the pancreatic duct (155,156). The LERV option is associated with a similar rate of successful CBDS clearance but lower incidence of post-ERCP pancreatitis in comparison to traditional ERCP (157–159). In addition, LERV seems associated with shorter hospital stays than the two-stage approaches (158). The main disadvantage of the LERV technique is the logistical and organisational problems that remain for performing intraoperative ERCP in the operating theatre (159).

2.3 CHOLECYSTECTOMY

2.3.1 Open Cholecystectomy

The first cholecystectomy was performed by Carl Langenbuch in Berlin in 1882 (160). Nowadays, most OC is performed through a right subcostal (Kocher) incision. Also, an upper midline incision is widely used. Classically, the retrograde technique, wherein the gallbladder is mobilised from its fundus towards the porta hepatis, is employed. The anterograde approach, from porta hepatis towards the fundus, has gained popularity in recent years among younger surgeons because of their laparoscopic experience (161). Nevertheless, the retrograde technique is particularly strongly indicated when severe inflammation is present.

During OC, the biliary tract can be assessed with palpation, IOC, or intraoperative ultrasonography. In OC, the IOC is typically performed via cystic duct or via needle puncture to the CBD. Nowadays, routine IOC is not recommended (162) and open surgery is regarded as the last resort or even obsolete therapy for CBDS. However, according to a recent meta-analysis, open CBDE seems superior to ERCP in achieving CBDS clearance without increasing morbidity (20% vs. 19%) or mortality (1% vs. 3%) (153).

The technique for mini-laparotomy cholecystectomy is quite comparable to standard OC, but it employs a more focused exposure. Mini-laparotomy cholecystectomy is performed through a 4–7 cm transverse incision a couple of fingerbreadths inferior to the xiphoid process. Mini-laparotomy cholecystectomy seems comparable to LC in terms of safety and recovery from surgery (163) and for its long-term outcome (164), but the technique is still not widely used.

Currently, OC is used mainly when the procedure is converted to an open one during LC or because LC is contraindicated or when cholecystectomy is performed in conjunction with another open abdominal procedure. Additionally, OC is still performed particularly often for elderly patients (7,21) and in cases of acute cholecystitis (8,23).

2.3.2 Laparoscopic Cholecystectomy

In 1985, E. Mühe performed the first LC, in Germany (165). Laparoscopic cholecystectomy became popular in the early 1990s and is now considered the gold standard for the treatment of symptomatic gallstone disease (13,166,167).

In the American LC technique, the surgeon is positioned to the left of the patient, whereas the French approach places the patient in a split-leg position with the surgeon standing between the patient's legs. The standard technique employs four ports, the position of which depends on which of these two techniques is used. In the American

technique, the camera port is usually placed in the periumbilical region, the operating port in the epigastrium, and both the liver retractor and the grasper in the upper right quadrant. In the French technique, the camera port is still in the periumbilical region, but the operating port is typically placed in the upper left quadrant, the liver retractor in the epigastrium, and the grasper in the upper right quadrant. The American and the French techniques are reported to be comparable in safety, if correctly used (12).

The anterograde (from porta hepatis towards the fundus) technique of dissection is typically used in LC. Laparoscopic cholecystectomy is still associated with an increased risk of BDI when compared to the OC of the pre-laparoscopic era. The occurrence of BDI often is associated with failure to clearly identify the anatomy of the triangle of Calot (see Figure 2), formed by the cystic duct, cystic artery, and common hepatic duct (168). The 'critical view of safety' concept was created to describe the most important step in the avoidance of BDI during LC (169). This refers to clearing the triangle of Calot and completely individualising, identifying, and isolating the cystic duct and artery before dividing them.

In LC, IOC offers detailed visualisation of the biliary anatomy, including the biliary tree proximal to the biliary bifurcation. Routine use of IOC may decrease the risk of BDI, but the evidence is inconclusive (162,171). However, IOC should be performed if BDI is suspected. Additionally, the incidence of unsuspected retained CBDS is about 4%, and only 15% of these recurrences proceed to cause clinical problems (172). Accordingly, routine IOC in LC is not recommended (162). However, in surgical training programmes, a policy of routine IOC may be supported by the need to train residents in how to perform that portion of the procedure (173). A cholangiogram is typically performed via the cystic duct in LC, and the skills developed and maintained via routine IOC provide a platform for progression to transcystic clearing of the CBD.

Laparoscopic CBDE, in expert hands, is reported to be at least as effective as ERCP in treatment of CBDS (143). The LERV procedure (discussed in detail in Subsection 2.2.4) combines laparoscopic and endoscopic techniques for CBDS management and appears to have an effectiveness similar to that of traditional ERCP while offering greater safety (157–159). In laparoscopy, CBD clearance is usually attempted by 'water flush'. This procedure may be performed through the cystic duct, if it is large enough, or through vertical choledochotomy. If the water flush manoeuvre fails, choledochotomy may allow a choledochoscopy and CBDS retrieval via Dormia basket. The feasibility of laparoscopic CBDE depends on several patient-specific variables, including tissue status (inflammation,

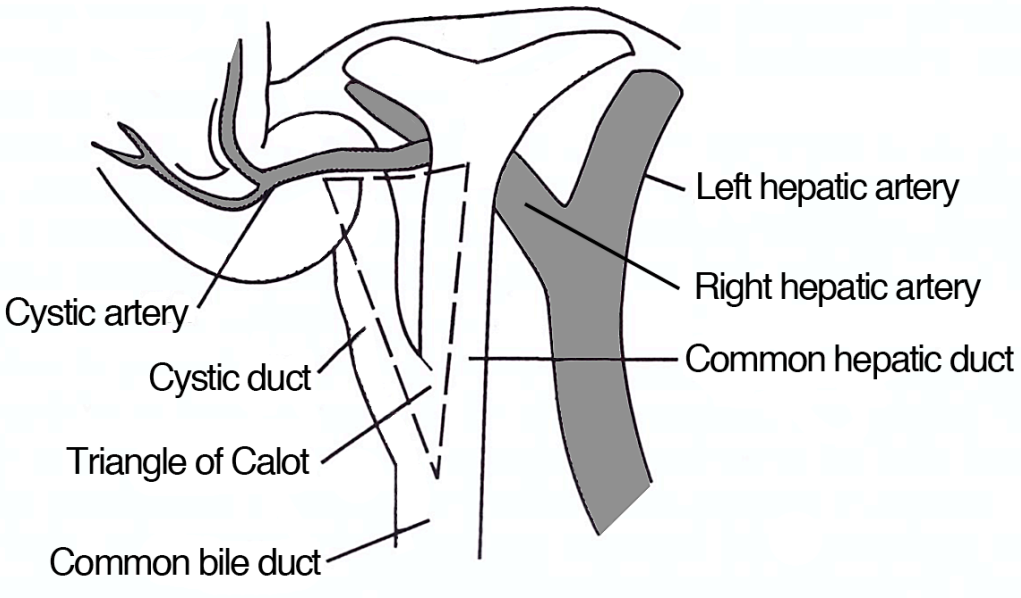

Figure 2. Anatomy of the triangle of Calot (figure modified from McAneny, 2008) (170).

adhesions, etc.), biliary anatomy (length, size, and insertion of the cystic duct and the size of the CBD), and characteristics of the CBDS (the stones' quantity, size, and location) (143). In addition, the need for special skills and instruments has limited the diffusion of laparoscopic CBDE beyond specialist centres.

New techniques to even minimise LC have been proposed lately, including natural orifice transluminal surgery, or NOTES, both transgastric and transvaginal, and single-incision laparoscopic surgery. In addition, several fewer-than-four-port LC techniques have been introduced. However, the benefits of these techniques over traditional four-port LC have yet to be proved (174).

2.3.3 Indications and Contraindications

The indications for surgery have remained the same for LC as they were for OC in the pre-laparoscopic era, with symptomatic and complicated gallstone disease being the most important indications (171). Complicated gallstone disease, no doubt, remains a clear indication. Another clear indication, though rare, is acute acalculous cholecystitis.

The timing of surgery in cases of acute cholecystitis has been a matter of debate. Two main approaches have been proposed: early surgical management and initial conservative management with antibiotics for resolution of inflammation, followed by delayed laparoscopic cholecystectomy. Early LC for acute cholecystitis has been proved safe by meta-analyses (175–178). It also shortens the hospital stay (175–177,179) and seems to be associated with lower costs (179–181) than delayed surgical management is. In a recent randomised multi-centre trial, early LC (within 24 hours) was associated with significantly lower morbidity than the delayed approach. This indicates that early LC in cases of acute cholecystitis may be superior management for stable patients without complications (179).

The role of symptomatic gallstone disease as a clear indication for cholecystectomy can be questioned. About 10–40% of patients continue to experience significant symptoms after cholecystectomy. This is often referred to as post-cholecystectomy syndrome (182,183). Atypical symptoms seem more likely to persist after cholecystectomy (184,185). Therefore, most cases involve a confusion with other functional disorders, such as irritable bowel syndrome (IBS) and dyspepsia, rather than a cholecystectomy-related entity *per se* (183,186). Additionally, in a recent systematic review of randomised controlled trials comparing cholecystectomy and observation for symptomatic gallstones, approximately half of the patients in the observation group did not require surgery or suffer complications during the follow-up of 14 years (187). These findings indicate that observation may be a valid alternative to surgery.

Biliary dyskinesia is defined as a rare disorder of the gallbladder characterised by pain and impaired gallbladder function in the absence of morphological changes (188). Initially, a single randomised controlled trial demonstrated positive outcomes in all 10 patients with biliary dyskinesia treated with cholecystectomy (189). Later, a longitudinal cohort study demonstrated a similar rate of symptom resolution during conservative therapy in more than 80% of patients with biliary-type symptoms but no gallstones (190). This resolution rate is comparable to the improvement described after surgery for symptomatic gallstone disease. Another study presentation reported a symptom-resolution rate of 50% after LC in carefully selected patients with biliary dyskinesia as compared to the 16% result seen in patients with non-surgical treatment after the follow-up period of four years (191). Nevertheless, biliary dyskinesia has become increasingly common as an indication for cholecystectomy among young, privately insured patients in the US, and it has been reported to account for up to 20% of cholecystectomies in adults at certain centres (192,193).

Given the natural progression of gallstone disease (discussed in Subsection 2.2.3), observation is a suitable policy for most patients with asymptomatic gallstone disease, and, in general, asymptomatic gallstones are not considered an indication for surgery (124).

There are certain groups of asymptomatic patients who may benefit from surgery (see Table 2, below); however, epidemiological studies have demonstrated an unfavourable risk–benefit ratio and no evidence of impact on gallbladder cancer for prophylactic cholecystectomies (133,135,182). In conclusion, the current literature seems to advocate restricting rather than expanding indications for cholecystectomy.

Table 2. Indications for cholecystectomy in cases of asymptomatic gallbladder disease (content modified from Sakorafas et al., 2007) (124).

Clear indications
Risk of malignancy: • The presence of large (≥3 cm) gallstones • Gallstones associated with gallbladder polyps >1 cm in diameter • A calcified (porcelain) gallbladder • Membership of some ethnic groups / living in an area with a high prevalence of gallbladder cancer associated with gallstones (American Indians; Mexican Americans; the Maori population of New Zealand; and residents of Colombia, Chile, and Bolivia)
Gallbladder stones associated with CBDS
Being a transplant patient (before or during transplantation)
Having a chronic haemolytic condition
Relative indications
Increased risk of conversion from asymptomatic to symptomatic disease: • Gallstones >2 cm in diameter • Small gallstones (<3 mm) • A non-functioning gallbladder
Diabetes mellitus
Symptoms of dyspepsia in the presence of gallstones
Questionable indications
Incidental cholecystectomy during another abdominal operation

The most common contraindications for LC are related to comorbid conditions that make the patient unable to tolerate general anaesthesia, such as serious cardiopulmonary diseases (171). Relative contraindications for LC include generalised peritonitis, septic shock, severe acute pancreatitis, untreated coagulopathy, advanced cirrhosis with failure of hepatic function, suspected gallbladder cancer, and previous abdominal operations that preclude a minimally invasive approach (171).

In contrast to the early days of laparoscopic surgery, the first and third trimester of pregnancy are no longer considered contraindications of LC. With its lower risk of spontaneous abortion and pre-term delivery relative to OC, LC has become the treatment of choice in pregnant patients with symptomatic gallbladder stones, no matter the trimester (194). A high recurrence rate of biliary colic and, more importantly, the significant gallstone-associated morbidity during pregnancy favour surgical treatment over non-operative management in pregnant patients with symptomatic gallbladder stones (194,195).

Laparoscopic cholecystectomy may be performed safely in patients with acute cholecystitis, but there are cases in which primary OC might be safer (171). For instance, LC is not a feasible option for all patients with gangrenous cholecystitis (196). In critically ill patients with acute cholecystitis, radiographically guided percutaneous cholecystostomy is an effective temporising measure until the patient recovers sufficiently to undergo cholecystectomy (197,198). Indications for primary OC also include known dense adhesions in the upper abdomen, known gallbladder cancer, and the surgeon's preference.

2.3.4 Conversion

Laparoscopic cholecystectomy cannot always be completed safely, and conversion to open procedure may be required. Conversion should be considered not a complication of LC but a means to avoid complications and ensure the safety of the patient (199). According to the literature, the conversion rate typically varies between five and 10 per cent (7,9,19,20,24,25,199), but single-centre cohorts with a substantially lower conversion rate have been reported (200,201).

Conversions from LC to OC can be either elective conversion or enforced (emergency) conversion (168). Elective conversion is defined as the decision by the surgeon to switch from the laparoscopic to the open approach at any stage in the operation before being forced to do so. In contrast, enforced conversion is an intraoperative emergency when the surgeon has to convert to laparotomy because of a severe iatrogenic injury, uncontrollable bleeding, or technical difficulty. Enforced conversion is associated with higher postoperative morbidity and mortality than elective conversion is (9,168).

The common reasons for conversion include inflammation, adhesions, unclear anatomy, and a complication or suspicion of one (18,19,199,200). Bleeding and BDI are the typical complications associated with conversion (18,19,199,200). Individual surgeons must make the decision on converting to an open procedure in line with their intraoperative assessment and experience, weighing the severity of inflammatory changes, the anatomical clarity, and their skills and comfort in proceeding (161).

Additionally, suspected CBDS has been reported to account for up to 8% of conversions in some studies (19,199), while in many other study results CBDS is not listed among the reported reasons for conversion (18,200,202). This finding is consistent with the fact that no consensus has been reached on CBDS management (143).

Known risk factors for conversion to OC include acute cholecystitis (9,168,203–205), previous upper abdominal surgery (168,199,203,204), male gender (9,24,168,199,203,204), obesity (9), higher age (24,168,203,204), bleeding (168), BDI (168), and CBDS (168). Compared to completed LC, conversion is associated with higher morbidity (7,168,199) and longer hospital stays (9,168,199,202).

Laparoscopic subtotal cholecystectomy seems to be a feasible and safe treatment option for severe cholecystitis (206,207). In the pre-laparoscopic era, open subtotal cholecystectomy was established as a safe and feasible procedure for cases of severe cholecystitis. In subtotal cholecystectomy, the gallbladder is resected towards the hepatoduodenal ligament. When further dissection becomes unsafe, the Hartmann's pouch is closed, after removal of gallstones, in a laparoscopic procedure typically employing an endoscopic linear stapler or an endo-loop (161,208). It is quite infrequently used but, as an alternative to conversion to OC, can reduce the morbidity associated with open laparotomy. Laparoscopic subtotal cholecystectomy may also reduce the incidence of BDI (206).

2.3.5 Complications

When compared to OC, LC is associated with lower mortality (7,8) and morbidity (6,7). In LC, the reported mortality varies between 0.06% and 0.5% (7,8,22,24), whereas the reported mortality associated with OC in the laparoscopic era varies between 0.8% and 4.9% (7,8,22,24,209,210). However, the higher mortality rates in OC are at least partly attributable to confounding factors, since OC is more often performed on high-risk patients (22,23).

Morbidity rates of 4.8–6.4% have been reported for LC and of even 19–34% for OC with minor complications included (7,209). In addition, a poorer outcome for converted patients has been reported than found for patients undergoing primary OC. This suggests that some patients with several risk factors for conversion might benefit from a primary OC procedure (209). Bile duct injuries and bleeding, both major complications, are discussed in sections 2.3.5.2 and 2.3.5.3.

In particular, the likelihood of wound problems and cardiopulmonary complications is much lower after LC than with the traditional open approach (211). Laparoscopic cholecystectomy also carries a lower risk of postoperative infection, the average rate of wound infections being 0.4–1.1% (17), whereas in OC the average rate is 1.4–5.4% (7,10).

According to meta-analyses of randomised controlled trials, prophylactic antibiotics do not prevent infections in low-risk patients undergoing LC (212,213). They may, however, reduce the incidence of infectious complications in high-risk patients (persons aged > 60 years; diabetics; and those with jaundice, acute cholecystitis, cholangitis, or acute biliary colic within 30 days of the operation) (212). Therefore, the routine use of preoperative antibiotic prophylaxis in LC is not recommended (171).

In a new era, with emphasis on minimally invasive surgery, experience in performing open biliary surgery is diminishing (161,210,214). This has influenced the outcomes of cholecystectomy-related procedures. For instance, the complication rate associated with open CBDE increased from 3.4% to 17.4% between 1979 and 2001 in the US (215).

2.3.5.1 Risk Factors for Complications

Large population-based studies have identified several risk factors for complications in cholecystectomy, including higher age (216,217); male gender (217); and, in cases of LC, surgeon inexperience (168,217,218) and low case load (217), as well as a prolonged operation (218,219).

Reports from training centres suggest that a learning curve for LC exists. Tang and Cuschieri (168) have posited a learning curve on the order of 200 operations for LC, with continued steady improvement by 40%, before the plateau of proficiency is reached, whereas, in a Swiss analysis of 22,953 LC procedures (218), the risk of intraoperative local complications was higher if the surgeon had performed 11–100 LC procedures than if he or she had carried out more than 100, suggesting that an individual surgeon has a learning curve of over 100 procedures. Additionally, in a US analysis of 33,309 cholecystectomies, about 20% of all complications were attributable to surgeons who had performed 200 or fewer cholecystectomies in the preceding five years (217).

The longer the operation, the higher the risk of complications seems to be in LC. In a large register study, the cumulative risk of perioperative complications was found to be four times higher if LC lasted more than two hours as compared to 30–60 minutes (218). In another study, prolonged duration of LC (over three hours) was associated with increased risk of complications – namely, BDI and bleeding (219). A ‘difficult cholecystectomy’ was likely to result in not only prolonged duration of the operation but also an increased risk of complications.

In large population-based studies, patients being older (8,22,216,220), male gender (8), emergent surgery (8,22,216), perioperative complications (22,216), and the open approach (22,23,220) have been associated with an increased risk of death among patients undergoing cholecystectomy. In 2000–2003, patients undergoing OC in Sweden had a 90-day mortality risk that was four times the risk of the general Swedish population, while the 90-day mortality risk for patients undergoing LC was lower than that of the general population (23). However, in 2007–2010, the 30-day mortality rate for cholecystectomy (including both LC and OC) was no different from that of the age- and gender-matched Swedish general population, indicating low cholecystectomy-related mortality (22).

2.3.5.2 Bile Duct Injury

Iatrogenic BDI is a complication highly specific to cholecystectomy. These injuries are associated with increased morbidity and mortality. The incidence of major BDI increased after the invention of LC, since which the incidence has slowly declined but not entirely disappeared. The current rate of major BDI in LC has stabilised at 0.1–0.6% (12,218,221–224). In contrast, while the rate remained at 0.1–0.2% in the era when OC dominated (11),

the rate of BDI in OC has risen in the laparoscopic era, coming to 0.29–1.46% when minor injuries are included (13,17,222,224,225).

Several factors have been associated with bile duct injury, including surgeon experience (217), patient age (221,224), gender (221,224), and acute cholecystitis, although the effect of the last of these on BDI rates remains subject to debate (12,175,224).

Surgeons who had performed 1–50 cholecystectomies were 2.4 times more likely to create a BDI than those who had performed more than 300 cholecystectomies over the previous five years. Surgery complexity was another factor associated with increased risk of BDI (217). However, other authors have not found a relationship between the experience of the surgeon and the incidence of BDI (226,227). Also, a BDI risk is always present, independently of the surgeon's skills and experience.

Nevertheless, the incidence of BDI in LC depends on the classification system used. Some studies consider only major bile duct injuries, while other works have also reported cystic duct leaks and minor leakage from the gallbladder bed. Several BDI classification systems have been proposed.

In the pre-laparoscopic era, biliary strictures were classified via the Bismuth system (228), which considers the level of healthy biliary mucosa available for anastomosis. The Strasberg classification is similar to the Bismuth but includes a few additional injuries seen more commonly in LC (169).

The Amsterdam scheme for classification of bile duct injuries was introduced in 1996 (229). It is the simplest of the classification systems, but it fails to describe the level of the injury or cover additional injuries. In the Amsterdam system (see Figure 3), type A refers to leakage from the cystic duct or peripheral hepatic radicles, type B to major bile duct leakage with or without concomitant biliary stricture, type C to bile duct stricture without leakage, and type D to complete transection of the duct. Injuries of type A are considered minor, while types B, C, and D are deemed major injuries.

Most of the classification schemes attach a specific injury (occlusion, division, partial, or complete) to a specific anatomical level, while these injuries can, in fact, occur almost anywhere and in a variety of ways. In addition, the lack of universal and comprehensive classification has led to variations in the definition of BDI in previous reports. To address these inconsistencies and variations, the European Association for Endoscopic Surgery (EAES) formulated a new, comprehensive classification based on existing systems, with the aim of having a single, all-inclusive, universally accepted classification system (230). The latter scheme grades BDI on the basis of the following elements: anatomical location within the biliary tree, type of division (complete, major, partial, or minor), presence of concomitant vascular lesion, presence of loss of substance, time of detection, aetiopathogenesis, and presence of occlusion (ligation or clip) or leaking.

The most important concomitant vascular lesion is injury to the RHA. It has been reported to increase mortality and decrease the success of the biliary repair (231–235). Right hepatic artery injury (RHAI) usually co-occurs with transection or injury to the right hepatic duct, and up to 60% of injuries to the right hepatic duct are accompanied by a concomitant injury to the RHA (233). In rare cases, associated injuries to other arteries and portal veins may occur also (233).

Fewer than half of the major bile duct injuries that occur are recognised during the primary operation (12,225,237). If a major bile duct injury occurs, whether detected at the time of the primary operation or instead in the postoperative period, the outcome is improved with early recognition and immediate referral of the patient to experienced attending surgeons for further diagnosis and treatment (171). Repair should not be attempted by the primary surgeon unless he or she has significant experience in biliary reconstruction (12,222,238). Greater experience in biliary reconstruction seems to be associated with an increased likelihood of survival in patients with BDI (238).

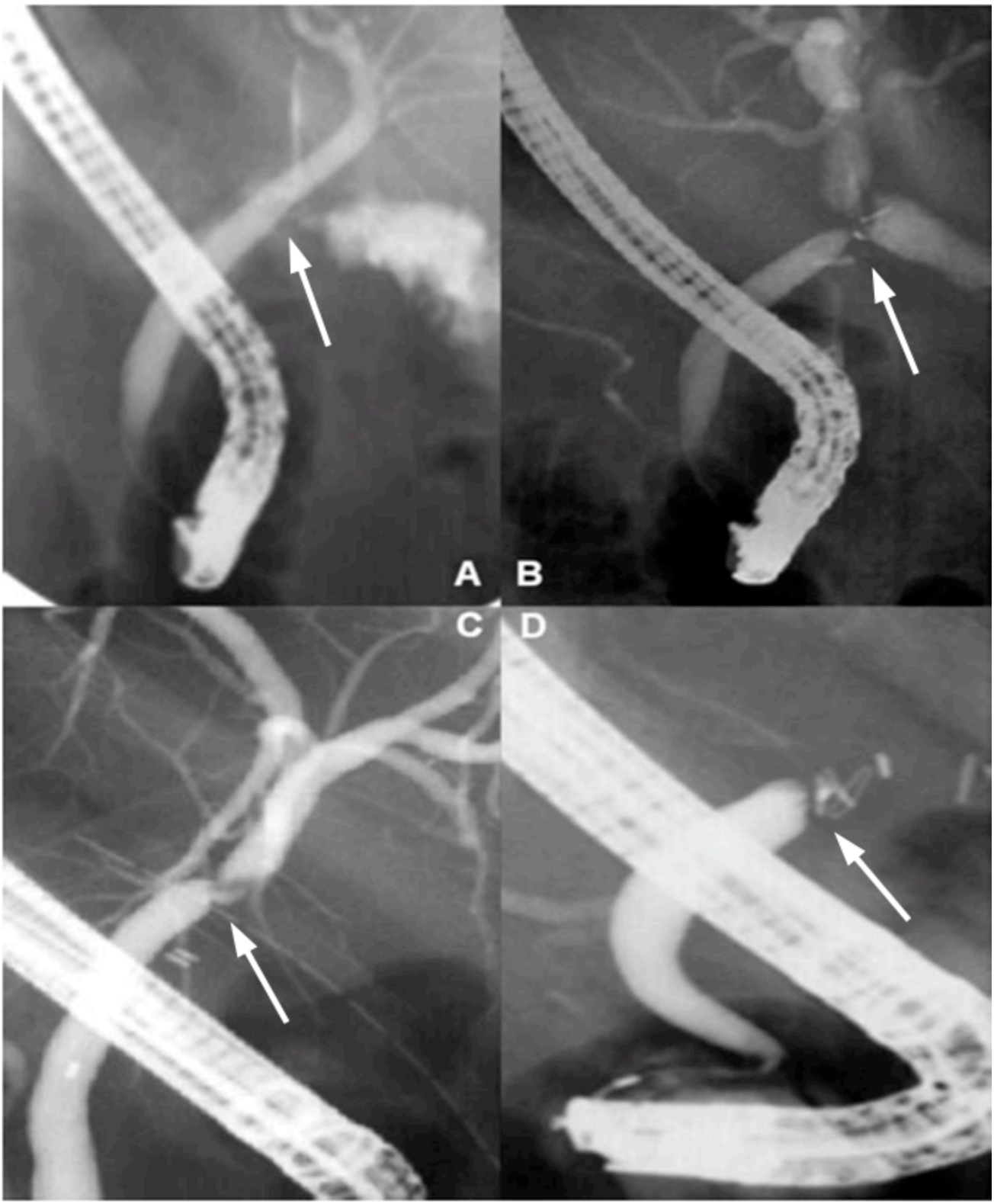

Figure 3. The Amsterdam classification of bile duct injuries (types A, B, C, and D). Type A: Leakage from the cystic duct or peripheral radicals. Type B: Major bile duct injury with leakage. Type C: Bile duct stricture without leakage. Type D: Complete transection or excision of the common bile duct. Figure modified from Nordin et al., 2011 (236). Reproduced with permission from the copyright-holder.

When a major bile duct injury occurs during OC or LC, mortality increases nearly tenfold (222). The need for biliary reconstruction confers a significant risk of anastomotic stricture requiring secondary surgical or radiologic interventions, and secondary biliary cirrhosis may develop. In a small subset of patients, BDI may eventually necessitate liver

transplantation (237). A recent meta-analysis indicates that BDI has a long-term detrimental effect on mental-health-related quality of life in patients undergoing LC (239).

Most injuries of Amsterdam type A, B, and C can be treated endoscopically with relatively high success rates, while type D BDI is an absolute indication for reconstructive surgery, usually hepaticojejunostomy (225). The long-term outcome of hepaticojejunostomy after BDI has been reported to be good in 83–85% of patients, but anastomotic strictures develop in 9–17% and up to 9% of patients eventually develop secondary biliary cirrhosis (240,241).

A concomitant vascular lesion – namely, RHAI – is a negative prognostic factor for BDI repair (231–235). Although isolated occlusion of the RHA rarely results in clinically significant hepatic ischaemia (233,242), RHAI when accompanied by BDI carries a higher risk of hepatic ischaemia (approximately 10%), most likely due to associated damage to the collateral vessels (243,244). Management of RHAI remains a matter of some debate. The conventional recommendation is that early repair of the artery be performed whenever possible (231,234,235,243,244). However, only 10% of patients with combined RHAI and BDI develop clinically significant hepatic ischaemia. This implies that the outcome is good in the majority of cases without reconstruction of the artery (244). The alternative strategy involves ligation of the RHA and allowing slow infarction to take place in a minority of patients, with its treatment via liver resection, if necessary (233,243–245).

Even though such injury is considered minor, a short-term BDI-related mortality rate as high as 4.2% has been reported for LC patients with type A BDI (246). In a US cohort with nearly 1.6 million cholecystectomies, patients with major BDI requiring biliary reconstruction were nearly three times more likely to die within 10 years than patients undergoing cholecystectomy without BDI (238).

2.3.5.3 Bleeding Complications

The focus in the literature has been on biliary complications of LC. Yet major bleeding remains a rare but serious complication of laparoscopy and cholecystectomy, showing an association with a poorer patient outcome (11,14,15). In addition, bleeding is still a frequent reason for conversion (15,16,18,22). For instance, in the analysis of 5,884 LC procedures presented by Bingener-Casey and colleagues (2002), bleeding accounted for 14% of all conversions.

The lack of systematic classification of bleeding complications in LC makes comparing the results described in published studies challenging. Some authors have assessed and reported only major vascular injuries (usually encompassing injuries to the aorta and its main branches, the vena cava, and the portal vein). Major vascular complications, while rare, are the most serious complications of laparoscopy (12,13,14,15)), although life-threatening bleeding may also occur from the liver bed (14). Vascular injuries may also be reported as trocar injuries. Other authors have documented bleeding that requires either transfusion or repeat operation or less serious intraoperative and postoperative bleeding. Intraoperative and postoperative bleeding are sometimes further divided into internal (within the peritoneal cavity of the retroperitoneal space) and external (of the abdominal wall) bleeding, on the basis of the localisation.

The incidence of postoperative intra-abdominal bleeding has been reported to be 0.69–1.05% in LC patients (17,20). In an analysis of 10,174 LC operations in Switzerland (20), bleeding was the most frequent intraoperative complication, occurring in 1.97% of the cases considered.

With respect to OC, few studies have reported the incidence of bleeding complications in the laparoscopic area. Roslyn and colleagues (11) reported the overall incidence of bleeding complications to be 0.4% in their analysis of 42,474 OC procedures. In their series, intraoperative bleeding was associated with a significant risk of death.

Previous studies have seldom reported on the need for blood transfusions related to bleeding complications of LC and OC. However, few publications reporting transfusion

rates for laparoscopic operations exist in general. In their analysis of 14,243 general laparoscopic operations (of which 59.4% were LC operations), Schäfer and colleagues (14) reported 33 patients with intraoperative and 63 patients with postoperative bleeding complications requiring blood transfusion. The overall rate of bleeding complications requiring transfusion was 0.7% in their series, while the overall rate of bleeding complications (including minor bleeding from, for example, laceration of minor vessels) was 4.1%. Opitz et al. (15) reported an overall bleeding rate of 3.3% in an LC-dominant (52%) sample of 43,028 general laparoscopic operations. In their study, a higher transfusion rate (24%) was observed for patients with postoperative bleeding as compared to patients with intraoperative bleeding (7%).

Several patient-specific predisposing factors for bleeding complications in cholecystectomy, such as anticoagulant or anti-platelet therapy or liver cirrhosis, exist. A high incidence of postoperative bleeding has been reported in patients on long-term anticoagulant therapy undergoing LC, even when the anticoagulant therapy had been discontinued long enough for the international normalised ratio to be reached (247).

It has been reported that systemic thromboprophylaxis in general surgery procedures is safe, resulting in only a slight increase in minor bleeding complications (248). In contrast, in a recent Swedish register-based study, systemic thromboprophylaxis increased the risk of bleeding complications in LC but the incidence of thromboembolic complications was not significantly reduced (249). However, thromboprophylaxis did not seem to increase the risk of bleeding in OC in that study. In general, the risk of developing postoperative thromboembolism after cholecystectomy appears to be low. An incidence of 0.03% has been reported for deep venous thrombosis and 0.06% for pulmonary embolism (250). The laparoscopic approach seems to be associated with a lower risk of postoperative thromboembolism than is open surgery (251). In conclusion, the verdict on systemic thromboprophylaxis during LC remains unclear.

Also, the association between anti-platelet therapy and bleeding complications is controversial, especially in the case of emergency surgery. In a recent retrospective case-control study, long-term aspirin anti-platelet therapy was not associated with increased risk of bleeding complications in emergent LC for acute cholecystitis (252). From the results, the authors concluded that long-term aspirin use should not be taken as an independent factor to delay emergent LC. Similarly, in a small retrospective study, clopidogrel anti-platelet therapy did not increase the morbidity associated with LC (253).

Lately, ultrasonic energy has been introduced as an advantageous alternative to electrosurgical energy for dissection in LC. Ultrasonic dissection has been proved safe (254). It seems to decrease blood loss during surgery (254,255), but more study is needed to assess its impact on the incidence of bleeding complications. New topical haemostatic agents may also help to ensure adequate haemostasis during laparoscopic cholecystectomy (256), but further studies are required for establishing their efficacy.

2.3.6 Cholecystectomy in Diabetic Patients

Although diabetes is associated with an increased risk of gallstone disease (113), only a few studies have assessed the outcome of LC in diabetic patients. Laparoscopic cholecystectomy for diabetic patients seems to be associated with higher mortality and morbidity (257), and also with longer hospital stays (258) than encountered with non-diabetic patients. However, similar outcomes in terms of morbidity (258) and length of hospital stay have been reported too (257).

The effect of diabetes on conversion rate remains subject to debate. Some authors have reported higher conversion rates in diabetic patients undergoing LC as compared to non-diabetic patients (203,257), while others have found no significant differences (204,258).

In cases of acute cholecystitis, diabetics are more likely to exhibit severe pathological findings, such as gangrenous changes and perforations of the gallbladder wall, than non-

diabetics are (259–261). Higher mortality and higher incidence of cardiovascular and renal complications have been reported for diabetic patients with acute cholecystitis undergoing cholecystectomy than among non-diabetics (259). Insulin treatment was associated with an even poorer outcome when compared to oral medication in the same study. However, diabetic patients were more likely than non-diabetics to undergo OC, a fact that may have an effect on mortality and complication rates. In contrast, other authors have reported a comparable or only slightly greater operative risk in diabetic patients with acute cholecystitis than in non-diabetic controls (132,133). These findings justify reconsideration of prophylactic cholecystectomy in asymptomatic diabetic patients with gallstones.

In general, the timing of surgery in cases of acute cholecystitis is subject to controversy (171,175). In a recent study (262), low-risk, American Society of Anesthesiologists (ASA) class I or II diabetic patients with acute cholecystitis had a significantly higher risk of surgical site infection and significantly longer hospital stays if cholecystectomy was delayed (by 24 or more hours from admission to hospital) in comparison to early (within 24 hours) cholecystectomy.

2.3.7 Cholecystectomy in Surgical Training

Training should equip surgeons to undertake both OC and LC confidently (263–265), but the decreasing frequency of OC in clinical practice may cause a reduction in training opportunities for residents. For example, in the US, the trend of declining numbers of open operations has affected biliary procedures especially strongly (266).

In addition, the total number of common surgical procedures, including LC, has been reported to vary between surgical residents in Denmark (267). In particular, there was substantial variation in the number of LC procedures performed independently.

Typically, before performing LC, surgical residents assist in some 15–20 LC operations (268). In addition, simulator and animal-model training are often used prior to performing LC (269). Several studies have reported comparable results in LC performed by surgical residents and by attending surgeons with careful patient selection and when surgical residents were assisted by attending surgeons (267,269–271), though the mean operating time has been reported to be longer for surgical residents than attending surgeons in some studies (269–271). Also, similar complication rates have been reported in five common general-surgery procedures (bowel resection, LC, hernia surgery, mastectomy, and appendectomy) in comparison between those performed by surgical residents and by attending surgeons, when the surgical residents were adequately supervised (272).

Today, BDI continues to occur for surgeons who have already completed the learning curve (226,227). If residents do not receive valid instruction and teaching for OC, conversion is not as easy as it might seem. A successful outcome in difficult cases requires familiarity with specific open techniques, which may be limited in the current training programmes both in the UK and in the US (161,214,265). In 2004, a chief surgical resident graduating in the United States had performed, on average, 12 OC procedures and fewer than two CBDE operations during residency, as compared to approximately 90 LC operations (161).

Schulman et al. (214) reported an average of 13 OC and 1.3 open CBDE operations per resident in the course of residency at a single centre in the US. At their centre, CBDE performed during OC accounted for only 5% of all open bile duct procedures. Proceeding from this finding, the authors recommended strong hepatobiliary exposure in residency programmes, whenever available, to ensure an adequate number of open biliary procedures during residency. Experience gained in other procedures wherein the gallbladder is removed or the CBD is transected or reconstructed, including pancreato-duodenectomy, hepatic lobectomy and biliary bypass or reconstruction, can provide some level of competency in OC and open CBDE, along with the repair of related injuries. Animal models and simulator training have also been proposed for overcoming this gap in

surgical training (98). With respect to LC, there is a growing body of evidence indicating that skills acquired during simulator training may be transferable to the operative setting (273,274). However, the impact of simulator training on actual patient outcome needs further assessment.

2.4 SUMMARY OF THE LITERATURE REVIEW

Statins may decrease the risk of gallstone formation (120,121), but further studies are needed to confirm these findings, and the impact of statin use on cholecystectomy rate at population level remains unknown.

Few studies have assessed the outcome of LC in diabetic patients. Laparoscopic cholecystectomy seems to be associated with higher mortality and morbidity in diabetic patients than non-diabetic patients (257). However, comparable outcomes in terms of morbidity have been reported (258). In addition, the effect of diabetes on conversion rate remains subject to debate (203,204,257,258).

The incidence of bleeding complications requiring transfusion or re-operation has been reported to be relatively low in patients undergoing LC (275). As for OC, in turn, very few studies have reported the incidence of these complications in the laparoscopic era. Very few published data are available on rates of transfusion of red blood cells (RBCs) and other blood components and on hospital costs linked with bleeding complications of LC and OC.

The declining number of OC procedures means that surgeons' experience with the open technique is tending to become more and more limited. The appropriate ratio of OC to LC in surgical training, for simultaneously minimising serious iatrogenic bile duct injuries, is unknown (161). In addition, outcomes of LC performed independently by surgical residents have not been reported.

3 *Aims of the Research*

The purpose of the dissertation project was to compare outcomes between laparoscopic and open cholecystectomy in the management of symptomatic gallstone disease. The specific aims of the individual studies were the following:

Study I: To analyse the outcomes of LC and OC procedures performed by surgical residents at a Finnish teaching hospital, with special focus on the occurrence of BDI

Study II: To examine the outcomes of LC and OC operations in diabetic patients

Study III: To analyse the impact of obesity, ageing, diabetes, and statin use on the rate of cholecystectomies in a Finnish population-based cohort and in a community-based hospital district (with a population of 110,000)

Study IV: To assess bleeding complications and transfusions associated with LC and OC in a Finnish register-based cohort

4 Patients and Methods

All of the patients in studies I and II and the patients in the hospital district-based cohort in Study III were treated at Mikkeli Central Hospital between January 1995 and December 2008. The study period began in the year when the first LC was performed at Mikkeli Central Hospital. After exclusion of cholecystectomies performed on known malignancies (n = 34) or as a part of other surgery (n = 30), the dataset for analysis comprised, in total, 2,565 cholecystectomies performed at the hospital from January 1995 to December 2008. Of these cholecystectomies, 1,581 were LC operations and 984 were OC procedures. The demographic and operative data of the cholecystectomy patients are shown in Table 3. The mean age of the LC patients was 53 years, 74% of them were female, and 80% belonged to ASA class I or II. Among the patients who underwent OC, the mean age was 65 years, 53% were female, and the most common ASA class was III (46%).

LC was the primary choice of treatment for gallbladder stone disease except very early in the study period. An attending surgeon decided between OC and LC on the basis of clinical and imaging findings. Eighty-five per cent of the LC procedures were elective operations, while only 27% of the OC operations were elective in nature. The most common reasons for primary OC were previous open upper abdominal surgery, generalised peritonitis, and findings of severe acute or chronic cholecystitis in the imaging studies.

Table 3. Demographic and operative data for the 2,565 patients who underwent cholecystectomy at Mikkeli Central Hospital in 1995–2008.

	Laparoscopic cholecystectomy (n = 1,581)	**Open cholecystectomy (n = 984)**
Females	1,169 (74%)	520 (53%)
Mean age (range), years	53 (8–92)	65 (13–97)
Mean BMI (range), kg/m^2	28 (16–75)	27 (15–60)
ASA category		
I	605 (38%)	172 (18%)
II	662 (42%)	278 (28%)
III	308 (19%)	455 (46%)
IV	6 (1.0%)	79 (8.0%)
Elective/emergent	1,346/226 (85%/14%)	266/718 (27%/73%)
Intraoperative cholangiography	365 (23%)	845 (86%)
Common bile duct exploration	48 (3.0%)	257 (26%)
Conversion	119 (7.5%)	–

ASA = American Society of Anesthesiologists
BMI = body mass index

The standard four-port technique for LC, either the French version (with the surgeon between the legs of the patient) or the US approach (surgeon on the left side of the patient), was used. The pneumoperitoneum was established by means of a Veress needle (>95%) or open Hasson technique. In LC, dissection was performed anterogradely. Open cholecystectomy was performed via the retrograde technique. Whilst IOC was always attempted in cases of OC, it was attempted only in selected cases of LC (e.g., when there was suspicion of choledocholithiasis or unclear anatomy): IOC was performed in 86% (n = 845) of the OC procedures but only 23% (n = 365) of the LC operations. Common bile duct exploration was performed in 26% (n = 257) of the OC cases. No laparoscopic CBDE

procedures were performed, and 3.0% (*n* = 48) of the LC patients underwent CBDE after conversion. The overall conversion rate was 7.5% (*n* = 119). The two most common reasons for conversion were unclear anatomy and bleeding.

4.1 LAPAROSCOPIC AND OPEN CHOLECYSTECTOMY IN SURGICAL TRAINING (STUDY I)

In the surgical training programme of Mikkeli Central Hospital, a non-university teaching hospital, second- and third-year surgical residents (*n* = 20) began their introduction to gallbladder surgery by assisting attending surgeons in both OC and LC procedures (5–10 operations in all). After that, each resident performed approximately 3–5 OC and 5–10 LC operations with the assistance of attending surgeons. After this training period, the residents performed 10–30 (mean: 20) LC operations independently during their third to fourth year of surgical training. The decision that the resident was able to perform cholecystectomy independently was always made by an attending surgeon. During the study period, nine attending surgeons, specialising in general or gastrointestinal surgery, performed cholecystectomies. Six of the attending surgeons were experts in LC, and the other three mainly performed OC operations. Elective operations were scheduled for the residents and the attending physicians by the secretary of the surgical ward. In cases of acute cholecystitis and persistent biliary colic requiring hospital admission, the surgeon on call operated on the patients.

The demographic data of the patients included in Study I are presented above and in Table 3. The Amsterdam system for classification of bile duct injuries (229) was used in this study.

4.2 LAPAROSCOPIC AND OPEN CHOLECYSTECTOMY IN DIABETIC PATIENTS (STUDY II)

Nine per cent (*n* = 227) of the cholecystectomies at Mikkeli Central Hospital between January 1995 and December 2008 were performed on diabetic patients. Of these diabetic patients, 102 underwent LC and 125 underwent OC. For Study II, the diabetic patients were grouped into those with type 1 and type 2 diabetes, on the basis of their medical history. Type 1 was defined as onset of diabetes before the age of 30 in combination with initial and subsequent insulin treatment. The remaining patients, with onset of diabetes after reaching age 30, were considered to have type 2 diabetes (treated by means of diet only, oral medication, and/or insulin). A few patients showed overlapping characteristics, and they were classified mainly as having type 2 diabetes; these few patients had little effect on the overall results.

In the above-mentioned group of 227 diabetic patients considered in this study, 127 (56%) were female and 100 were male, and the mean age was 68 ± 12 years. The patients' mean BMI was 29 ± 6.1 kg/m^2, and 68% (*n* = 155) of the patients belonged to ASA classes III and IV. Ten per cent (*n* = 23) of the patients had no other comorbidities in addition to diabetes, while 51% (*n* = 116) had two or more other comorbidities. Twenty per cent (*n* = 45) of the diabetics were classified as having type 1 diabetes, and the rest (*n* = 182) were classed as type 2 diabetics.

4.3 THE IMPACT OF OBESITY, AGEING, DIABETES, AND STATIN USE ON CHOLECYSTECTOMY RATE (STUDY III)

To assess the impact of obesity, ageing, diabetes, and statin use on the rate of cholecystectomies in Finland between 1995 and 2009, a population-based register cohort was compiled. The numbers of LC and OC procedures and the respective discharge diagnoses were obtained from the National Institute for Health and Welfare (NIHW) registry. The weight changes of the population were obtained from a previous study and the population's age changes from Official Statistics of Finland. The number of diabetic patients was obtained from Finland's national drug reimbursement register. For purposes of the study, a diabetic patient was defined as a person who received drug reimbursement for any glucose-level-lowering drug. The drug reimbursement register has nearly 100% coverage of patients receiving glucose-lowering drugs in Finland, but this register does not cover undiagnosed or dietary-treatment-only patients. The details on the population's statin use are based on the reimbursement for prescribed statins between 1995 and 2009 in Finland and were retrieved from the nationwide Prescription Register of Finland and the dataset from an earlier study (276).

For more in-depth understanding of the causative risk factors for LC, also the retrospective cohort of 1,581 LC procedures performed at Mikkeli Central hospital in 1995–2008 was analysed. The demographic and operative data of this cohort are presented above and in Table 3.

4.4 TRANSFUSION RATES ASSOCIATED WITH LAPAROSCOPIC AND OPEN CHOLECYSTECTOMY (STUDY IV)

The Optimal Use of Blood (VOK) registry was a joint effort of the Finnish Red Cross Blood Service and 10 out of Finland's 21 hospital districts. Five of the participating hospital districts were teaching-university-connected districts (C, F, G, I, and J in Figure 4), and five were central hospital districts (A, B, D, E, and H in the figure). Data from potential transfusion patients were collected from existing, unconnected databases for a separate VOK register. The VOK registry was continually updated between 2002 and 2011, but the registry has since been permanently terminated, and the data were erased in 2012. The data-collection method has been presented by Palo et al. (277).

For Study IV, patients who visited any VOK hospital district for LC or OC between 1 January 2002 and 31 December 2007 were extracted into a separate research registry. In that registry, data from hospital district J are available only for 1 January 2004 to 31 December 2007. In addition to demographic and operative details, data on blood-component use related to cholecystectomies were collected. The data gathered included the number of red blood cell units transfused, number of transfused platelets (PLTs), number of transfused fresh frozen plasma products (FFP and Octaplas®), and total cost of the transfused blood components. In Finland, FFP was available from the beginning of the study until midway through 2007. During the study period, Octaplas® was available from 2005 until the end of the period. The use of FFP and Octaplas® are presented separately because the unit size and therefore the per-unit quantity of coagulation factors are smaller in Octaplas® than in FFP.

In total, 22,117 cholecystectomies performed in the participating hospital districts in 2002–2007 were included in Study IV. This number accounts for 43% of all cholecystectomies carried out in Finland in 2002–2007. Seventy-eight per cent of the cholecystectomies (17,175) were LC operations, and 22% (4,942) used OC. Demographic and operative data for these patient cases are shown in Table 4. In the LC group, the mean age was 53 years, 73% of the patients (12,473) were female, and the most common ASA class was category II (38.0%, n = 6,424). In the OC group, the mean age was 63 years, 51% of the patients (2,513) were female, and the most common ASA class was III (35.5%, n = 1,756).

About 88% of the LC procedures (15,114) were elective operations, while only 38% of the OC operations (or 1,870) were.

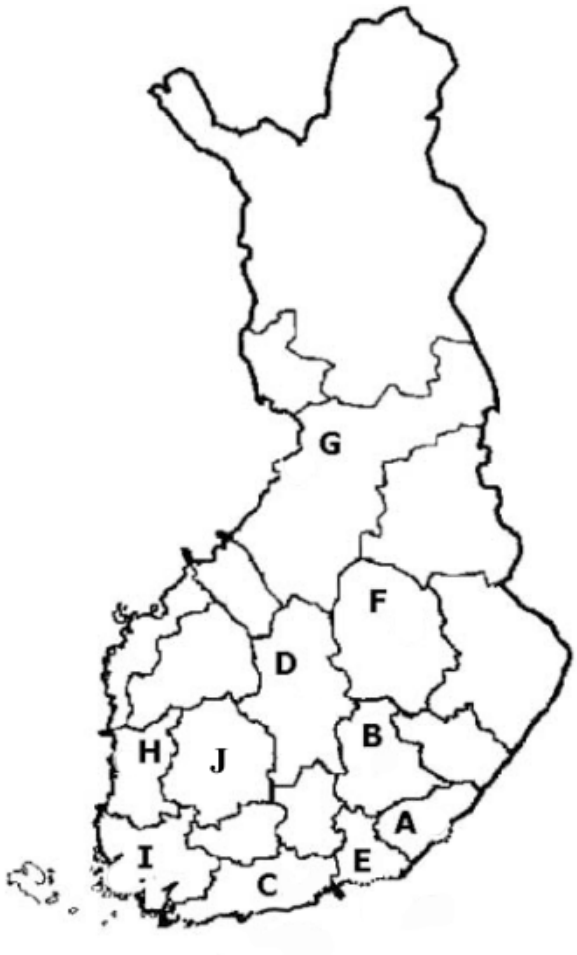

Figure 4. Hospital districts in the Optimal Use of Blood register and Finnish hospital districts. Figure reproduced from the original publication IV under Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

4.5 STATISTICS

In all four of the studies, the distribution fitting of the data was initially analysed with the Kolmogorov–Smirnov test. The independence of two categorical variables was tested for with a χ^2 test, and the mean values of continuous variables were compared via either Student's *t*-test or the Mann–Whitney U test, as appropriate. In Study I, a χ^2 test was used for comparing categorical variables and ANOVA for comparison of mean values of continuous variables between three groups.

In Study II, the odds ratio (OR) was used to estimate the relative risk of postoperative complications. The factors associated with postoperative complications were determined via univariate and multivariate binary logistic regression models with a forward selection process. The following factors were included in the regression analysis: the type of diabetes, the type of surgery, the presence of acute cholecystitis, and comorbidities.

Statistical significance was defined as a *p*-value below 0.05. All statistical analyses were performed with SPSS for Windows, version 17.0 (from SPSS, Inc., of Chicago, IL, US; 2008) in studies I, III, and IV and version 18.0 (SPSS, Inc., of Chicago, IL, US; 2009) in Study II.

4.6 ETHICS-RELATED ASPECTS OF THE WORK

The study protocols were approved by the medical director of Mikkeli Central Hospital (for studies I–III), the institutional review board of the Finnish Red Cross Blood Service (Study IV), and the VOK steering group (Study IV).

Table 4. Demographic and operative data for 22,117 patients who underwent cholecystectomy in 10 of the 21 member hospital districts covered by Finland's VOK registry in 2002–2007. Data reproduced from the original publication IV under Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

		LC ***n* = 17,175 (%)**	**OC** ***n* = 4,942 (%)**	***p***
Males/females		4,702/12,473 (27/73)	2,429/2,513 (49/51)	<0.001
Mean age ± SD (range)		52 ± 15 (16–94)	63 ± 15 (16–97)	<0.001
ASA category*	I	5,842 (34.0)	673 (13.6)	<0.001
	II	6,424 (38.0)	1,564 (31.6)	<0.001
	III	2,753 (16.0)	1,756 (35.5)	<0.001
	IV	183 (1.1)	409 (8.3)	<0.001
	V	0 (0.0)	31 (0.6)	<0.001
Elective/emergency		15,114/2,018** (88/12)	1,870/3,039*** (38/62)	<0.001
Mean operative time ± SD, minutes		70 ± 37	99 ± 50	<0.001
Intraoperative cholangiography		862 (5.0)	1,009 (20.0)	<0.001
Common bile duct exploration		156 (0.9)	369 (7.5)	<0.001
In-hospital mortality		59 (0.3)	122 (2.5)	<0.001
Length of hospital stay ± SD, days		2.8 ± 2.4	8.0 ± 4.7	<0.001

ASA = American Society of Anesthesiologists

SD = Standard deviation

* Data missing for 1,974 patients in the LC group and 509 patients in the OC group

** Data missing for 43 patients

*** Data missing for 33 patients

5 Results

5.1 LAPAROSCOPIC AND OPEN CHOLECYSTECTOMY IN SURGICAL TRAINING (STUDY I)

Of the 2,565 cholecystectomies, a third were performed by the surgical residents independently during the study period. The median numbers of operations performed independently per resident (n = 20) were 15 OC procedures and 25 LC procedures, 25 elective operations and 15 emergency operations.

The demographic data of the cholecystectomy patients are compared by category of operating surgeon in Table 5. The number of female patients was lower for the assisted operations than the operations performed by residents and attending surgeons. Compared to the other groups, the patients operated on by attending surgeons were younger. The patients in the assisted operations belonged to higher ASA classes and had acute cholecystitis more often than did the patients in the other groups.

When one considers LC only, the total rate of complications, including bile duct injuries and mortality, was similar across the various surgeon groups: 12% (n = 57) for trainees vs. 16% (47) for assisted vs. 11% (n = 89) for specialists (see Table 6). The median duration of LC was significantly longer for the residents operating independently and the assisted groups than for the attending surgeons. The conversion rate was higher for the assisted group (14%, n = 41) than the other groups (7.0% (n = 34) for trainees and 5.5% (n = 44) for specialists) (see Table 5). The LC patients operated on by attending surgeons underwent re-operation more often than the patients in the other surgeon categories.

In all, BDI occurred in 11 cases (0.7%) in LC. There were 10 Amsterdam type A injuries: eight cystic duct leaks and two leaks from the duct of Luschka. Two patients with cystic duct leaks were successfully treated via ERCP and endoscopic sphincterotomy (ES). One patient treated initially by ERCP, ES, and biliary stenting underwent laparotomy and T-tube application at a later stage because of biliary peritonitis. Seven patients with type A bile duct injuries underwent laparotomy and suturing for successful treatment. Eight of the 11 patients with BDI were operated on by attending surgeons, and the others were operated on by surgical residents assisted by attending surgeons. All these attending surgeons were experienced in biliary surgery. No injuries meeting the criteria for Amsterdam type C were observed.

Only one patient had severe, Amsterdam type B BDI (0.06%) after conversion to OC: an 82-year-old male whose elective LC was converted early to OC. He had a history of biliary pancreatitis. In this case, bile duct injury was suspected intraoperatively. Intraoperative cholangiography was performed but revealed no sign of bile duct injury. A small incision injury to the common bile duct resulting in perihepatic abscess was discovered in laparotomy five days later. This was successfully treated via suturing and T-tube application. There were no severe (Amsterdam type B, C, or D) bile duct injuries associated with laparoscopically completed cholecystectomies. No complete transections or excisions of the common bile duct (cases of type D BDI) were observed. The management of BDI associated with LC has been reported upon in more detail by Paajanen and colleagues (278).

As with LC, the mean duration of OC performed by surgical residents both independently and with the assistance of attending surgeons was longer (see Table 7). Overall morbidity did not differ significantly between the surgeon classes in OC. Only two bile duct injuries occurred in OC operations: One leakage from a cystic stump (Amsterdam type A BDI) was

Table 5. Data of the patients undergoing cholecystectomy, categorised by operating-surgeon class (data reproduced from the original publication I with permission from the copyright-holder).

	Trainee alone (*n* = 822)	**Assisted (*n* = 754)**	**Specialist alone (*n* = 989)**	***p***
Females	569 (69%)	462 (61%)	658 (67%)	<0.010
Median age, years (interquartile range)	60 (48–70)	63 (49–75)	56 (43–67)	<0.001
Median BMI (interquartile range)	27 (25–31)	27 (24–30)	27 (24–30)	n.s.
ASA category				
I	226 (28%)	167 (22%)	380 (38%)	<0.0001
II	340 (41%)	247 (33%)	353 (36%)	<0.010
III	237 (29%)	289 (38%)	237 (24%)	<0.0001
IV	19 (2.0%)	51 (7.0%)	19 (2.0%)	<0.0001
Acute cholecystitis	290 (35%)	408 (54%)	247 (25%)	<0.0001

BMI = Body mass index

ASA = American Society of Anesthesiologists

Table 6. Perioperative data and outcome of laparoscopic cholecystectomies (*n* = 1,581) (data reproduced from the original publication I with the permission of the copyright-holder).

	Trainee alone (*n* = 485)	**Assisted (*n* = 302)**	**Specialist alone (*n* = 794)**	***p***
Median operative time, minutes (interquartile range)	80 (65–100)	80 (60–110)	55 (40–75)	<0.0001
Median bleeding, ml (interquartile range)	10 (0–45)	10 (0–50)	10 (0–30)	n.s.
Conversion rate	34 (7.0%)	41 (14%)	44 (5.5%)	<0.0001
Complications (all)	57 (12%)	47 (16%)	89 (11%)	n.s.
Repeat operations	1 (0.2%)	2 (0.7%)	19 (2.4%)	<0.010
Wound infections	11 (2.2%)	13 (4.3%)	11 (1.4%)	<0.050
Postoperative hernias	6 (1.2%)	5 (1.7%)	7 (0.9%)	n.s.
Bile duct injuries[1]				
Amsterdam A	0	3 (1.0%)	7 (0.8%)	n.s.
Amsterdam B–D	0	0	1 (0.1%)	n.s.
Mortality	1 (0.2%)	0	1 (0.1%)	n.s.
Median hospital stay, days (interquartile range)	3 (3.0–4.0)	4 (3.0–5.0)	3 (3.0–4.0)	n.s.
Postoperative ERCP	13 (2.7%)	14 (4.6%)	28 (3.5%)	n.s.

[1] Bile duct injuries were classified in line with the Amsterdam classification scheme

managed via endoscopic stenting. One Amsterdam type B BDI occurred in a patient with difficult infection of the gallbladder. The resultant hepatic duct laceration was treated by endoscopic stenting. Mortality related to OC was 1.9% overall and was significantly higher in the assisted operations (see Table 7).

Table 7. Perioperative data and outcome of open cholecystectomies (*n* = 984) (data reproduced from the original publication I with the permission of the copyright-holder).

	Trainee alone (*n* = 337)	**Assisted (*n* = 452)**	**Specialist alone (*n* = 195)**	***p***
Median operative time, minutes (interquartile range)	90 (75–115)	90 (65–120)	65 (50–91)	<0.0001
Median bleeding, ml (interquartile range)	200 (150–300)	250 (150–400)	150 (100–300)	n.s.
Complications (all)	45 (13%)	66 (15%)	24 (12%)	n.s.
Re-laparotomies	8 (2.4%)	13 (2.9%)	5 (2.6%)	n.s.
Wound infections	18 (5.3%)	14 (3.1%)	18 (9.2%)	<0.010
Postoperative hernias	14 (4.2%)	16 (3.5%)	9 (4.6%)	n.s.
Bile duct injuries[1]				
Amsterdam A	0	0	1 (0.5%)	n.s.
Amsterdam B–D	0	1 (0.2%)	0	n.s.
Mortality	3 (0.9%)	14 (3.1%)	2 (1.0%)	<0.050
Median hospital stay, days (interquartile range)	7 (6–9)	9 (7–12)	8 (7–12)	n.s.
Postoperative ERCP	15 (4.5%)	29 (6.4%)	10 (5.1%)	n.s.

[1] Bile duct injuries were classified in accordance with the Amsterdam classification scheme

5.2 LAPAROSCOPIC AND OPEN CHOLECYSTECTOMY IN DIABETIC PATIENTS (STUDY II)

Out of the 227 cholecystectomies performed on diabetic patients, almost half (49%) were emergency operations, mainly because of acute cholecystitis. In cases involving type 1 diabetes, 66% of the patients (30/45) underwent an emergency operation, while the corresponding rate for type 2 diabetes was 44% (81/182; $p = 0.012$). During the study period, 45% of the diabetics were operated upon with laparoscopic technique. However, the percentage of cholecystectomies performed on diabetic patients that were LC operations increased towards the end of the study period (35% in 1995–2001 vs. 55% in 2002–2008; $p = 0.002$).

Demographic data of the diabetic patients who underwent LC and OC are presented in Table 8. Compared to the LC patients, the OC patients were older, more often male, and more often operated on for reason of acute cholecystitis. The OC patients also belonged to higher ASA classes and had type 1 diabetes and renal and cardiac comorbidities more often than the LC patients did. In preoperative laboratory findings, the mean plasma-glucose concentration was higher in the OC patients than in the LC patients (11 ± 5.5 mmol/l vs. 7.8 ± 2.7 mmol/l; $p < 0.0001$).

A conversion rate as high as 16% (16/102) was observed in diabetic patients undergoing LC. This was significantly higher than the corresponding figure for non-diabetic patients who underwent LC in the study hospital during the study period (7.0%; $p < 0.009$). Obesity was not associated with a higher conversion rate in diabetic patients.

The overall complication rate and the mortality rate were significantly higher in the OC group than in the LC group (see Table 9). No mortality or severe BDI was associated with LC performed on diabetic patients. Type 1 diabetes was more often associated with acute cholecystitis (30 vs. 45; $p = 0.012$), complications (22 vs. 45; $p = 0.006$), and mortality (5 vs. 4; $p = 0.017$) than type 2 diabetes was. Gangrenous cholecystitis, however, was not associated with an increased complication rate (41% vs. 29%; *p* not significant) or mortality (7.1% vs. 3.2%; *p* not significant) in diabetics.

Table 8. Patient characteristics in cases of laparoscopic and open cholecystectomy in diabetic patients (data reproduced from the original publication II with permission from the copyright-holder).

	Laparoscopic ***n* = 102 (%)**	**Open** ***n* = 125 (%)**	***p***
Males	35 (34)	65 (52)	<0.05
Mean ± SD age, years (range)	63 ± 12	71 ± 10	<0.0001
Acute cholecystitis	13 (13)	98 (78)	<0.0001
BMI, kg/m^2			
<30	60 (59)	85 (68)	n.s.
30–40	37 (36)	38 (30)	n.s.
>40	5 (5.0)	2 (2.0)	n.s.
Type 1 diabetes	12 (12)	33 (26)	<0.01
ASA category			
I–II	51 (50)	21 (17)	<0.0001
III–IV	51 (50)	104 (83)	<0.0001
Comorbidities			
None	15 (15)	8 (6.4)	n.s.
Cardiac	40 (39)	83 (66)	<0.0001
Pulmonary	12 (12)	9 (7.2)	n.s.
Hypertension	74 (72)	96 (77)	n.s.
Renal	7 (6.9)	41 (33)	<0.0001
Previous laparotomy	47 (46)	49 (39)	n.s.

Table 9. Operative data and outcome in cases of laparoscopic and open cholecystectomy in diabetic patients (data reproduced from the original publication II with the permission of the copyright-holder).

	Laparoscopic ***n* = 102 (%)**	**Open** ***n* = 125 (%)**	***p***
Conversion rate	16 (16)		
Mean ± SD operative time, minutes	82 ± 35	89 ± 44	n.s.
Mean ± SD bleeding, ml	80 ± 130	270 ± 200	<0.0001
Mean ± SD hospital stay, days	5.2 ± 3.4	11 ± 11	<0.0001
Choledochotomy rate	6 (6.0)	35 (28)	<0.0001
Cholangiography rate	28 (28)	107 (86)	<0.0001
Number of re-operations	1 (1.0)	6 (4.8)	n.s.
Operative complications	20 (20)	49 (39)	<0.01
Surgical-site infection	6 (6.0)	14 (11)	n.s.
Pulmonary	1 (1.0)	1 (1.0)	n.s.
Urinary	0 (0)	2 (2.0)	n.s.
Bleeding	1 (1.0)	2 (2.0)	n.s.
Miscellaneous	12 (12)	21 (17)	n.s.
Mortality	0 (0)	9 (7.2)	<0.01

In univariate analysis, type 1 diabetes, open cholecystectomy, higher ASA class, and multiple comorbidities were associated with increased risk of complications (see Table 10). In multivariate analysis, only renal insufficiency was a significant risk factor for operative complications. None of morbid obesity (BMI > 30 kg/m^2), acute cholecystitis, and the type of diabetes was associated with increased risk of complications.

5.3 THE IMPACT OF OBESITY, AGEING, DIABETES, AND STATIN USE ON CHOLECYSTECTOMY RATE (STUDY III)

In total, 123,794 cholecystectomies were performed in Finland between 1995 and 2009. Of these, 76.5% (94,740) were performed via laparoscopic technique. The annual rate of cholecystectomy, of all types, decreased by 13%, from 8,600 to 7,500, during the study period. The number of LC operations rose by 10% and the number of OC operations declined by 60% between 1995 and 2009 (see Figure 5). During the study period, the median rate of LC varied between 110 and 140 operations per 100,000 inhabitants.

During the study period, Finland's elderly population (>65 years of age) grew by 24%, from 732,417 to 910,441. In the same time, the number of elderly patients undergoing LC also increased, by 18% (from 1,248 to 1,473). Between 1995 and 2009, the nationwide mean BMI rose from 26.7 to 27.2 kg/m^2, and the percentage of the country's obese inhabitants (BMI > 30 kg/m^2) increased from 10.6% to 16% between 1995 and 2008. Also, the number of patients in Finland using glucose-lowering medication increased 41%, from 134,400 to 190,000, in this time.

Table 10. Univariate and multivariate regression analysis of risk factors for complications in cholecystectomy of diabetic patients (data reproduced from the original publication II with permission from the copyright-holder).

Factor		**Univariate analysis**			**Multivariate analysis**		
		Odds ratio	**95% CI**	***p*-value**	**Odds ratio**	**95% CI**	***p*-value**
Type of diabetes	(type 1/2)	0.474	0.191–0.733	0.004	0.622	0.293–1.320	0.216
BMI ≥ 30.1 kg/m^2	(yes/no)	1.026	0.570–1.846	1.000			
Previous laparotomy	(yes/no)	0.894	0.503–1.588	0.771			
Type of surgery	(laparoscopic/ open surgery)	0.366	0.200–0.670	0.001	0.622	0.312–1.238	0.176
Acute cholecystitis	(yes/no)	1.615	0.915–2.851	0.114			
ASA category	(I–II/III–IV)	2.640	1.333–5.229	0.005	0.123	0.438–2.390	0.958
Coexisting diseases (>1)	(yes/no)	0.888	0.329–2.392	1.000			
Multiple (>2) diseases	(yes/no)	3.799	2.054–7.028	0.001	2.118	0.983–4.562	0.055
Coronary heart disease	(yes/no)	1.671	0.938–2.975	0.085			
Pulmonary disease	(yes/no)	2.212	0.893–5.482	0.088			
Hypertension	(yes/no)	1.707	0.851–3.424	0.087			
Renal insufficiency	(yes/no)	5.792	2.988–11.45	0.001	3.048	1.397–6.653	0.005

BMI = Body mass index

CI = Confidence interval

According to a nationwide register-based study, the one-year prevalence of statin use rose elevenfold, from 7.8 per 1,000 inhabitants to 88.9 per thousand in Finland between 1995 and 2005 (147). The overall rate of statin use increased from 355 per 100,000 in 1995 to 1,772 per 100,000 in 2005. Among Finnish females, the incidence rose from 312 per 100,000 to 1,732 per 100,000. Among males, the increase was from 399 per 100,000 to 1,815 per 100,000.

In the community-based cohort of 1,581 LC procedures performed at Mikkeli Central Hospital in 1995–2008, the annual LC rate at first increased more than twofold from the initial rate of 48 per 100,000 inhabitants. However, the increase levelled off towards the end of the study period and the rate was 102 per 100,000 inhabitants at the end of the period, in 2008. The annual rates of LC operations overall and those performed on elderly (>65 years of age), obese (BMI > 30 kg/m^2), and diabetic patients are presented in Figure 6. The proportion of obese, elderly, and diabetic patients undergoing LC nearly doubled during the study period, but the increases were not statistically significant. At the same time, the number of patients using statins or other lipid-lowering drugs increased substantially (from 4.2% to 17%; $p < 0.001$).

The demographic data and outcomes for LC converted to OC at the study hospital are presented in Table 10. Conversions were more frequently performed for males, elderly patients, obese patients, diabetics, and patients who underwent an emergency operation. Compared to the laparoscopically completed cholecystectomies, the conversions were associated with a higher complication rate (see Table 11).

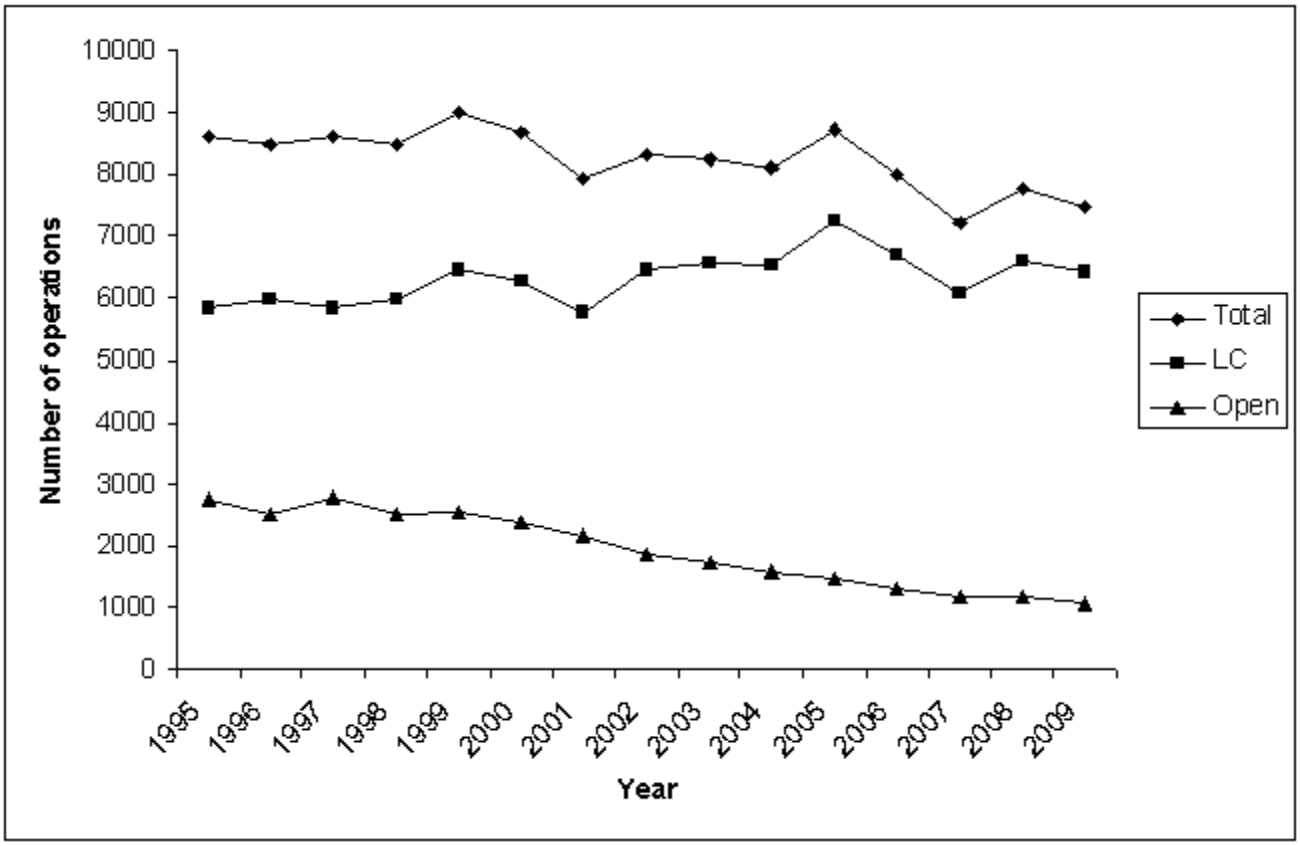

Figure 5. The number of cholecystectomies in Finland in 1995–2009. The total number of cholecystectomies ('Total'), laparoscopic cholecystectomies ('LC'), and open cholecystectomies ('Open') are presented. Figure reproduced from the original publication III (doi: 10.1177/1457496913492463, http://sjs.sagepub.com/content/102/3/158.long) by permission of the copyright-holder.

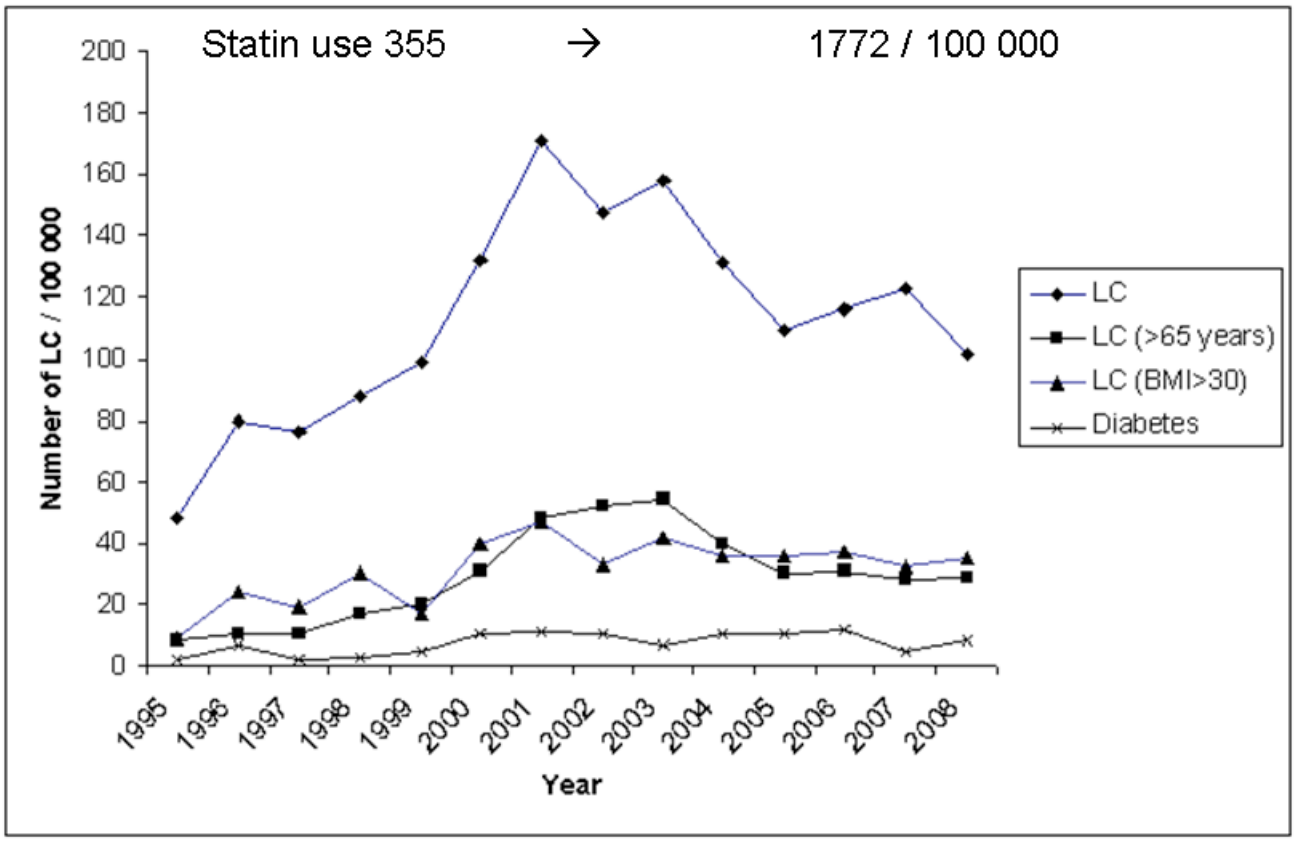

Figure 6. The total number of laparoscopic cholecystectomies performed ('LC') and that of LC operations performed in patients aged >65 years, obese (BMI > 30 kg/m^2) patients, and diabetic patients at the study hospital in 1995–2008. The overall incidence of statin use in Finland per 100,000 inhabitants in 1995 and 2005 is shown also. Figure reproduced from the original publication III (doi: 10.1177/1457496913492463, http://sjs.sagepub.com/content/102/3/158.long) with the permission of the copyright-holder.

Table 11: Comparison of laparoscopically completed cholecystectomies and conversions to open surgery in the study hospital (data reproduced from the original publication III (*doi: 10.1177/1457496913492463*, *http://sjs.sagepub.com/content/102/3/158.long*) with the permission of the copyright-holder)

	LC: *n* (%) *n*= 1,462	**Conversion: *n* (%) *n* = 119**	***p*-value**
Females	1,096 (75)	73 (61)	0.001
Mean age (years) ± SD	53 ± 15 (range: 8–92)	58 ± 16 (range:21–84)	0.001
Elderly status (>65 years)	356 (24)	50 (42)	<0.001
Mean BMI (kg/m^2) ± SD	28 ± 5.2 (range: 16–75)	29 ± 5.6 (range: 18–44)	0.006
BMI > 30 kg/m^2	388 (27)	49 (41)	0.001
Presence of diabetes	88 (6.0)	16 (13)	0.006
Emergency cases	186 (13)	40 (34)	<0.001
Wound infections	23 (1.6)	12 (10)	<0.001
Bleeding complications	16 (1.1)	2 (1.7)	n.s.
Postoperative hernias	10 (0.7)	8 (7)	<0.001
Bile duct injuries	9 (0.6)	2 (2)	n.s.

LC = Laparoscopic cholecystectomy
SD = Standard deviation
BMI = Body mass index
Statistical analysis was performed via Student's *t*-test or a χ^2 test

5.4 TRANSFUSION RATES IN LAPAROSCOPIC AND OPEN CHOLECYSTECTOMY (STUDY IV)

In the register-based cohort of 22,117 cholecystectomies, the LC patients were younger, were more often female, and more often underwent an elective operation than the OC patients (see Table 3). In the OC group, as many as 16% of patients received transfusion of blood components, of any type, as compared to 1.6% of the patients in the LC group (see Table 12). Similarly, the proportions of patients with RBC, PLT, FFP, and Octaplas® transfusions were significantly higher in the OC group than the LC group (again, see Table 12). In addition, the mean transfused dose of FFP was significantly higher in the OC group as compared to the LC group. However, the mean transfused dose of the other blood components (RBCs, PLTs, and Octaplas®) and the mean cost of the blood components per transfused patient did not differ significantly between the groups (as shown in Table 12).

In this cohort, 48 patients (0.002%) received massive transfusion, which refers to administration of 10 or more RBC units. The mean age of the massive-transfusion patients was 48 years, and 69% of them were male (see Table 13). Most cases (81%) were related to OC and emergent operations (72%). In addition to RBCs, 78% of the patients received fresh frozen plasma products (FFP or Octaplas®) and 46% PLTs. Massive transfusion was associated with marked in-hospital mortality (15%).

Table 12. Use of blood components in open cholecystectomy cases ('OC') and laparoscopic cholecystectomy cases ('LC') in 2002–2007 (data reproduced from the original publication IV under Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/)).

	LC	**OC**	
	***n* = 17,175 (%)**	***n* = 4,942 (%)**	***p***
Patients with RBC transfusion	216 (1.3)	641 (13)	<0.001
Mean transfused RBC dose, units (range)	3.4 (1–18)	3.6 (1–46)	n.s.
Patients with PLT transfusion	15 (0.1)	59 (1.2)	<0.001
Mean transfused PLT dose, units (range)	16 (4–48)	21 (3–104)	n.s.
Patients with FFP transfusion	74 (0.4)	241 (4.9)	<0.001
Mean transfused FFP dose, units (range)	3.2 (1–10)	4.3 (1–42)	0.008
Patients with Octaplas® transfusion	14 (0.1)	43 (0.9)	<0.001
Mean transfused Octaplas® dose, units (range)	3.2 (1–12)	4.2 (1–15)	n.s.
Patients with blood-component transfusion	276 (1.6)	774 (16)	<0.001
Mean cost of transfused blood components, euros (range)	284 (51–1,310)	394 (51–10,607)	n.s.

RBC = Red blood cell

PLT = Platelet

FFP = Fresh frozen plasma

Table 13. Demographic and operative data, and use of other blood-component products, in patients given massive RBC transfusion (≥10 units) (data reproduced from the original publication IV under Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/)).

		Patients receiving massive RBC transfusion ***n* = 48 (%)**
Males/females		33/15 (69/31)
Mean age ± SD (range)		48 ± 16 (34–90)
ASA category*	I	2 (4.2)
	II	7 (15)
	III	13 (27)
	IV	14 (29)
	V	7 (15)
OC/LC		39/9 (81/19)
Elective/emergency		13/34** (28/72)
Mean operative time ± SD, minutes		122 ± 74
Intraoperative cholangiography		8 (17)
Common bile duct exploration		6 (13)
Patients with PLT transfusion		22 (46)
Patients with FFP transfusion		30 (63)
Patients with Octaplas® transfusion		7 (15)
In-hospital mortality		7 (15)
Length of hospital stay ± SD, days		23 ± 14

ASA = American Society of Anesthesiologists
SD = Standard deviation
RBC = Red blood cell
PLT = Platelet
FFP = Fresh frozen plasma
* Data on ASA class missing for five patients
** Data missing for one patient

6 Discussion

6.1 LAPAROSCOPIC AND OPEN CHOLECYSTECTOMY IN SURGICAL TRAINING (STUDY I)

According to previous reports, LC performed on selected patients by surgical residents, when properly supervised, does not increase morbidity or compromise the surgical outcome (269,279). In the study reported upon here, the outcomes of the cholecystectomies performed by surgical residents independently were comparable to the overall patient outcome. The conversion rate was comparable to rates reported in the literature (7,9,20,25,199), and no bile duct injuries were observed in LC performed by the residents independently. However, attending surgeons may have operated on those patients with more complicated disease. At present, it would be unethical to perform a randomised study with similar patients between surgical residents and attending surgeons. If a 'difficult cholecystectomy' is suspected, the experienced surgeon's consultation is recommended both in the OC vs. LC decision-making process and during the operation, to minimise complications (161,218).

Study I demonstrates that OC and LC may still be complementary in surgical training programmes. On average, a surgical resident performed 15 OC procedures and 25 LC operations independently during his or her third and fourth year of surgical residency, as compared to an average of 12 OC operations per resident in the US during the entire period of residency in the early 2000s (161). The number of OC procedures is likely to be even smaller today. The important aspects seem to be adequate practice in both open and laparoscopic surgery and the assistance of an attending surgeon. Training should equip surgeons with the skills required to perform both open and laparoscopic cholecystectomy (263,264).

Evidence is accumulating that modern simulator training (namely, virtual-reality training) improves surgical residents' technical performance during laparoscopic surgery (274,280). Therefore, simulator training is increasingly incorporated into surgical training programmes. However, its impact on patient outcome is not known (280).

Successful patient selection (for both OC and LC) and quite liberal use of OC may be reasons for the low number of cases of severe BDI found to be associated with LC in Study II. Bile duct injuries occur even two to three times more often in LC than in the OC of the pre-laparoscopic era (11,12,218,221–224), with experienced surgeons being no exception (218). Therefore, it may still be a reasonable option to perform OC for severe acute cholecystitis, especially if the surgeon is inexperienced in LC.

BDI continues to occur for surgeons who have completed the learning curve (227). At the same time, experience in performing open biliary surgery is diminishing (161,210,214), which renders conversion no longer as easy as it might seem. A successful outcome in a difficult case requires familiarity with specific open techniques, which may be limited in current training programmes in the UK and US (161,214). The number of OC procedures is diminishing in Finland too, in a development that may pose a threat of inadequate exposure to open techniques in surgical training. Laparoscopic subtotal cholecystectomy seems to be a feasible option for compensation for the decline in experience of OC among the younger generation of surgeons in cases of severe cholecystitis. Laparoscopic subtotal cholecystectomy may reduce the OC-associated morbidity and even decrease the incidence of BDI (206). Additionally, performing LC early on (within 24 hours of hospital admission) for patients presenting with acute cholecystitis may reduce the number of 'difficult cholecystectomies'. Early LC for acute cholecystitis seems to reduce overall morbidity

relative to delayed-interval LC (179,281), but its impact on the occurrence of BDI remains to be seen.

6.2 LAPAROSCOPIC AND OPEN CHOLECYSTECTOMY IN DIABETIC PATIENTS (STUDY II)

Study II indicates that LC is a safe procedure for diabetic patients, with the complication rate being significantly lower than that in OC. In addition, there was no mortality in the LC group, in contrast to the mortality of 7.2% in the OC group. A fatal outcome was associated with older patients, open cholecystectomy, acute cholecystitis, type 1 diabetes, and multiple comorbidities. Therefore, early LC, before emergence of infection-linked complications, may be the optimal choice for diabetic patients with gallstone disease.

Acute cholecystitis in diabetes often results in gangrenous cholecystitis with perforation and biliary peritonitis (259–261). Accordingly, prophylactic cholecystectomy has been proposed for diabetic patients with asymptomatic gallstones. However, there are no studies showing that early LC in diabetic patients with asymptomatic or mild symptomatic gallstone disease could reduce the overall complications related to gallstone disease. In addition, comparable outcomes of cholecystectomy have been reported in cases of acute cholecystitis among diabetic patients and non-diabetics (260,261). In the study discussed here, the morbidity and mortality rates were higher with gangrenous cholecystitis but the differences were not statistically significant.

In Study II, many patients who might have intuitively benefited from a minimally invasive approach did not undergo LC. One of the reasons is that several diabetic patients were operated upon in an emergency procedure during on-call hours by general surgeons, not all of whom were familiar with laparoscopic technique. As more laparoscopy experience was gained, the number of LC procedures performed on diabetic patients increased during the second half of the study period. Evidently, hepatobiliary surgeons, usually experienced in laparoscopic technique, are most competent in performing LC in cases of gangrenous cholecystitis. However, they are not always available at non-specialist hepatobiliary centres, especially during on-call hours. Nevertheless, there are no prospective randomised studies comparing LC and OC in acute cholecystitis for diabetic patients. No severe BDI occurred in diabetic patients undergoing LC, a finding that may in part be due to successful selection between OC and LC for the individual patients.

The role of diabetes as a risk factor for conversion is still debated. Some authors have reported that diabetes is not associated with a higher risk of conversion (204,258,282), with several having found no significant differences, but diabetes was found to be significantly correlated with an increased conversion rate in other studies (203,257). In the study reported upon here, diabetic patients had a significantly higher conversion rate than did non-diabetic patients, with rates of 16% and 7.2%, respectively. Obesity has been linked to a higher conversion rate (9,283,284); however, obesity was not associated with a higher conversion rate among diabetic patients in this study.

Type 2 diabetes and obesity are both known risk factors for gallstone formation. When BMI exceeds 30 kg/m^2, the risk of gallstone disease is threefold that of subjects with lower BMI values (76). Previous studies indicate that LC is a safe, feasible, and efficient procedure in obese patients but remains quite technically demanding even in experienced hands (285,286). In Study II, morbid obesity in combination with diabetes was not associated with a higher risk of complications in cholecystectomy. Actually, the only factor that significantly increased the complication rate for diabetic patients undergoing cholecystectomy in multivariate regression analysis was renal disease. Similar findings have been reported for non-diabetic patients undergoing laparoscopic surgery (287,288).

Perioperative hyperglycaemia and poor preoperative control of diabetes (elevated glycosylated haemoglobin, HbA1c) have been reported to be correlated with increased risk

of complications among patients undergoing non-cardiac general surgery procedures (289–292). In Study II, the preoperative mean glucose concentration was higher in OC patients than in LC patients (neither postoperative glucose values nor HbA1c values were gathered). Still, the higher preoperative mean glucose concentration may have contributed to the higher morbidity and mortality in the OC group in this study of diabetic patients.

6.3 THE IMPACT OF AGEING, OBESITY, DIABETES, AND STATIN USE ON CHOLECYSTECTOMY RATE (STUDY III)

According to a previous report (293), the cholecystectomy rate in Finland increased by 15% between 1989 and 1991. This increase actually peaked one year before the general introduction of LC in Finland, which took place in 1992. A similar increase in cholecystectomy rate concomitant with the introduction of LC was observed in Sweden but not in other Scandinavian countries (293). In a US study, the share of OC in North Carolina dropped from 100% to 32% between 1988 and 1993 while LC progressed from non-existence to being the dominant approach for managing patients with gallstones, with the overall cholecystectomy rate remaining stable (294). Similarly, in other countries in the Nordic region, LC progressed from being a non-existent procedure in 1989 to the dominant approach in 1994, accounting for 61–78% of cases. In Finland, however, the diffusion of the new technology was slower and 28% of cholecystectomies in 1994 were performed with the laparoscopic approach (293). In the population-based analysis for Study III, the proportion of LC rose to 86% and the OC rate decreased dramatically in Finland between 1995 and 2009. However, the overall rate of cholecystectomies declined.

Nevertheless, there are reasonably large variations in cholecystectomy trends between hospitals and between regions (295,296). In the community-based cohort of Mikkeli Central Hospital, the rate of LC began increasing rapidly from 48 per 100,000 inhabitants in 1995. It peaked in 2001, and the increase levelled off with the figure reaching 102 per 100,000 in 2008. In a Norwegian community-based cohort, the cholecystectomy rate initially increased concomitantly with the introduction of LC between 1990 and 2003, then remained stable at a level of 107 per 100,000 between 2004 and 2011 (295). At Mikkeli Central hospital, the proportion of elderly, obese, and diabetic patients undergoing LC seemed to be rising during the study period. The results for this community-based cohort also confirmed the findings of earlier studies showing that acute cholecystitis, diabetes, male gender, ageing, and obesity are all important risk factors for conversion and a poorer outcome of LC (9,12,24,168,199,203–205,218).

The trend of an increase in LC would be an expected finding in light of the diffusion of technology over time as experience grew and the procedure's safety and efficacy became proven. Another reason for the increased LC rate may be lowering of the threshold for surgery in the laparoscopic era (297), which may result in expensive and unnecessary overtreatment. In a recent retrospective analysis, approximately 20% of cholecystectomies were found to have been performed with doubtful or no indication at an Italian centre after the introduction of LC (298). Although LC is a relatively safe procedure, it still carries a considerable, albeit relatively small, risk of major complications, such as severe BDI and major bleeding, associated with significant morbidity and mortality. In Finland, however, the operative treatment protocol or indications for cholecystectomy seem not to have changed substantially during the study period. The increased use of ERCP particularly in elderly patients may explain part of the reduction in cholecystectomy numbers.

Another reason may be an increased incidence of symptomatic gallstones leading to LC. The prevalence of gallstones is as great as 10–15% among the adult population of developed countries (1). During follow-up, about 80% of gallstones remain asymptomatic, 10% of patients who have them develop mild symptoms, and 10% develop severe symptoms leading to cholecystectomy (299). In Finland, as in other Western societies,

obesity, alcohol use, and comorbidities are increasing, and the population is ageing. This increase in the prevalence of known risk factors for gallstone disease at the population level may also have an effect on the LC rate.

The aetiology of symptomatic gallstones is associated with obesity and alcohol use, possibly in part through the effects of these on serum lipids (104,300). In the developed countries, approximately 80% of gallstones originate from cholesterol-supersaturated bile (1,4). Statins inhibit hepatic cholesterol biosynthesis; therefore, the long-term use of statins may be associated with a decreased risk of gallstones (120,121,301). The advent of LC has moved interest away from pharmacological treatment of gallstones. Nevertheless, recent studies have also raised the possibility that cholesterol-lowering agents inhibiting hepatic cholesterol synthesis (statins) or intestinal cholesterol absorption (ezetimibe) or drugs acting on specific nuclear receptors involved in cholesterol and bile acid homeostasis may, alone or in combination, offer an additional therapeutic tool for treating cholesterol-originated gallstones (120,121,302,303).

Although the prevalence of the risk factors for gallstone disease is increasing at population level, one explanation for the lack of increase in the overall cholecystectomy rate may be the substantial increase in the use of statins in Finland in recent years (276). Statin use has increased particularly among elderly patients. However, the evidence for an association between statins and gallstone disease is conflicting, and further studies are needed to assess the possible causal role of statins in symptomatic gallstone disease and the rate of cholecystectomies. In a recent case-control study, no difference between statin users and non-users was found in the severity of gallstone disease or in the outcomes after cholecystectomy, even though statin use is associated more often with comorbid conditions and polypharmacy (304).

6.4 TRANSFUSION RATES IN LAPAROSCOPIC AND OPEN CHOLECYSTECTOMY (STUDY IV)

In Study IV, open cholecystectomy was correlated with a higher rate of transfusion of blood components than LC was. Thirteen per cent of the OC patients received RBC transfusion. For the other blood-component products too (PLTs, FFP, and Octaplas®), transfusion rates were significantly higher in the OC group. In addition to the more invasive nature of OC, this may be partly due to the fact that the OC patients were older and hence might have been more likely to receive anticoagulant or anti-platelet therapy. However, the latter could not be confirmed, because of lack of data on anticoagulant or anti-platelet therapy in this study. The OC patients also underwent an emergent operation more often than LC patients did.

The lack of systematic classification of bleeding complications in LC makes comparison of the results of this study with those described in other literature challenging. In addition, previous studies have seldom reported on blood transfusion rates related to LC and OC. The transfusion rates for LC in this study, 1.3% for RBCs and 1.6% for any blood-component products, are higher than reported previously for LC-dominant general laparoscopy cohorts (14,15). About 30% of patients in these laparoscopy cohorts, however, underwent herniotomy or appendectomy, both procedures that do not involve the dissection of the liver bed, a potent source of bleeding. This may be one reason for the higher transfusion rate observed in Study IV. Additionally, it has been reported previously that the rate of RBC usage in Finland has been rather high in comparison to that in other European countries, partially because a sufficient supply of blood has meant that the availability of blood-component products is not limited and there is low risk of transfusion-transmitted viral infections in Finland (305).

The similar mean transfused doses and mean costs of transfused blood components per transfused patient in LC and OC cases found in this study indicate that the severity of

bleeding complications may not differ substantially between OC and LC. Nevertheless, the higher transfusion rate observed in OC increases the average costs of OC relative to LC. Current data on massive transfusion confirm the results of previous reports (11,14,15,306) indicating that major bleeding remains a rare but serious complication of laparoscopy and cholecystectomy with significant associated mortality. New advances of technology, such as ultrasonic dissection and anticoagulant pads, may decrease the bleeding complications found in future studies.

6.5 LIMITATIONS OF THE RESEARCH

There are several limitations to the research described here. It is based on retrospective and register data. Accordingly, the poorer outcome of OC observed in the study data is at least partly attributable to confounding factors. Open cholecystectomy was more often performed on older patients and in an acute setting. Similar findings have been reported for other retrospective and register-based studies of cholecystectomy (7,8,21–23).

Studies I–III utilised the retrospective cholecystectomy cohort of Mikkeli Central Hospital. The study period includes 1995, the year when the first LC was performed at this hospital. Therefore, in the early part of the study period – i.e., before the new technique was adapted – LC was not the primary choice of treatment for symptomatic gallstone disease. Additionally, the majority of emergent cholecystectomies (mainly for acute cholecystitis) were performed during on-call hours and roughly a third of the general surgeons on call were not experts in laparoscopic surgery and hence preferred the open approach throughout the study period. These factors naturally contribute to the selection bias.

Study IV used cholecystectomy data from the VOK register. Its register-based nature was one of the weaknesses of this study. Firstly, the current data cover only those transfusions associated with the hospital stay during which the cholecystectomy was performed, so cases of delayed postoperative bleeding requiring transfusion may have been missed. Also, repeat operations necessitated by bleeding or performed for any other reason were not reported. Thirdly, conversions could not be identified from the data, on account of the lack of a separate procedure code for conversion in the NCSP. Consequently, cases of LC converted to OC were included in the OC group in this study, although bleeding is a frequent reason for conversion (17–20).

In addition, the register-based nature of the study rendered it impossible to identify patient-specific risk factors for bleeding complications, such as anticoagulant therapy or liver cirrhosis, from the available data. However, the association between anti-platelet therapy and bleeding complications is subject to debate, especially in the case of emergency surgery (252). The impact of the new non-vitamin-K antagonist oral anticoagulants on the incidence of bleeding complications associated with LC is an interesting topic for future research.

High coverage (83–100%) and correctness rates (97–100%) have been reported for the Swedish Register for Gallstone Surgery and Endoscopic Retrograde Cholangiopancreatography (307) and the Danish Cholecystectomy Database (308). However, the VOK register, utilised in this study, is not a dedicated cholecystectomy or biliary surgery register; instead, it incorporated data from all potentially transfused patients, including surgical patients. The cholecystectomy cohort of the VOK register analysed in Study IV accounts for 43% of all cholecystectomies performed in Finland in 2002–2007. The validity of the cholecystectomy cohort of the VOK register has not been analysed. A previous study reported 96.8% concordance between the overall transfusion data of the VOK register and the sales data of the Finnish Red Cross Blood Service, the only blood-component provider in Finland, for the most commonly transfused adult blood components: RBC, PLT, and FFP products (277). Additionally, a concordance level of 97.5%

was reported for primary knee-replacement operations at participating hospitals, with more than 200 knee- or hip-replacement operations per year (277).

In conclusion, the main limitations of this research stem from the retrospective and register-based nature of the work. On the other hand, the tradition of randomised controlled trials in the field of general surgery is rather young. For instance, the initial acceptance of LC stemmed from the results of case-controlled studies, and more than 80% of general surgeons in the United States had adopted the procedure by 1992, before the results of any randomised controlled trials comparing LC and OC had been published (17,167). Scientific knowledge of cholecystectomy today remains mostly based on retrospective data and findings from small randomised controlled trials at best. The need for well-designed, adequately powered randomised controlled trials in relation to gallbladder surgery is evident.

7 Conclusions

I) Strategies for safe cholecystectomy, both laparoscopic and open, need to be formally addressed in surgical training programmes. With careful selection of patients, LC performed independently by surgical residents is safe.

II) Laparoscopic cholecystectomy is a safe procedure for diabetic patients with symptomatic gallstone disease. Although the rate of conversion to open surgery was elevated among diabetic patients, the complication rate was lower than or comparable to that in primary open cholecystectomy.

III) The rate of application of LC increased in Finland between 1995 and 2008, but the overall cholecystectomy rate remained stable or decreased slightly even though the prevalence of risk factors for symptomatic gallstone disease increased in the population examined. The impact of the substantial increase in statin use on the incidence of symptomatic gallstone disease warrants further study.

IV) LC is associated with lower rates of transfusion of blood components than OC is. The observation of similar mean transfused doses and similar mean costs of transfused blood components per transfusion-receiving patient in LC and OC operations indicate that the severity of bleeding complications may not differ substantially between OC and LC.

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