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Karolinska Institutet, Stockholm, Sweden

# SURGEON-PERFORMED ULTRASOUND AND TIMING OF SURGERY IN ACUTE CHOLECYSTITIS

Camilla Gustafsson

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# SURGEON-PERFORMED ULTRASOUND AND TIMING OF SURGERY IN ACUTE CHOLECYSTITIS

## THESIS FOR DOCTORAL DEGREE (Ph.D.)

The thesis will be defended at Södersjukhusets aula (Floor 6),
Friday 5 June 2020 at 09:00.

By


**Camilla Gustafsson**



*Principal Supervisor:*
**Associate Professor Anders Sondén**
Karolinska Institutet
Department of Clinical Science and Education Södersjukhuset
Division of Surgery

*Co-supervisors:*
**MD PhD Anna Lindelius**
Karolinska Institutet
Department of Clinical Science and Education Södersjukhuset
Division of Surgery

**MD PhD Martin Dahlberg**
Karolinska Institutet
Department of Clinical Science and Education Södersjukhuset
Division of Surgery

**Associate Professor Hans Järnbert-Pettersson**
Karolinska Institutet
Department of Clinical Science and Education Södersjukhuset

*Opponent:*
**Professor Bengt Isaksson**
Uppsala University
Department of Surgical Sciences
Division of Upper Abdominal Surgery

*Examination Board:*
**Professor Per Sandström**
Linköping University
Department of Biomedical and Clinical Sciences
Division of Surgery, Orthopedics and Oncology

**Associate Professor Inga-Lena Nilsson**
Karolinska Institutet
Department of Molecular Medicine and Surgery
Division of Endocrine Surgery

**Associate Professor Daniel Wilhelms**
Linköping University
Department of Biomedical and Clinical Sciences
Division of Drug research

*Even a stopped clock gives the right time twice a day*

Ride (Cool Your Boots; Going Blank Again 1992)

# Abstract

## Introduction

The use of bedside ultrasound has increased, as equipment has become accessible, user friendly, and ultrasound education is expanding in many specialties. The aim of this project was to validate surgeon-performed ultrasound and to optimise the surgical treatment for patients with acute cholecystitis, in particular in planning timing of surgery.

## Methods

Papers I-III represent prospective clinical studies where patients with gallstones, acute cholecystitis or appendicitis were included. Sensitivity, specificity, accuracy, and predictive values of surgeon-performed ultrasound were calculated for these diagnoses. Radiologist-performed ultrasound was used as reference for the diagnosis of gallstones (Paper I). In acute cholecystitis, internationally accepted criteria for the diagnosis were used as reference, and in appendicitis, operation logs were used to verify the diagnosis (Paper II).

In Paper III, patients with diagnosed acute cholecystitis were included and followed with repeated daily ultrasounds, during admission. The study had a descriptive design, where measures of the gallbladder wall, gallbladder volume, and gallbladder wall oedema were followed over time.

Paper IV consists of a register-based cohort study with retrospectively analysed data from the National Register for Gallstone surgery. Out-of-hours surgery was considered independent variable and the primary outcome was any complication within 30 days. Secondary outcomes were proportion of open procedures and operative time exceeding two hours. Logistic regression models were used to adjust for confounders.

## Results

Papers I and II: Sensitivity for surgeon-performed ultrasound was 88.2% in diagnosing gallstones. Specificity was 99.0% and the accuracy was 94.4%. The sensitivity for surgeon-performed ultrasound in diagnosing acute cholecystitis was 60.0%, specificity 98.6%, and accuracy 93.9%. For appendicitis the sensitivity was 53.3%, specificity 89.7%, and accuracy 77.3%.

Paper III: The gallbladder volume and gallbladder wall thickness were mostly stable over time, with a slight tendency to decrease among the 37 patients that received repeated examinations. The presence of gallbladder wall oedema did not change over time.

Paper IV: Out-of-hours cholecystectomy did not result in a higher proportion of complications 15.6% *versus* 13.6% (adjusted odds ratio 1.12 (95% CI 0.99-1.28)), but in a higher proportion of open procedures 37.9% *versus* 28.9% (adjusted odds ratio 1.39 (1.25-1.54)). There was a lower proportion of long procedures out of hours, 40.4% *versus* 55.8% (adjusted odds ratio 0.63 (0.58-0.69)).

## Conclusion

Surgeon-performed ultrasound can be used to diagnose gallstones with high accuracy. Diagnosing acute cholecystitis and appendicitis with ultrasound is more challenging, but examinations with a positive test can help to confirm a clinically suspected diagnosis. The use of ultrasonography in preoperative risk scoring for acute cholecystitis needs to be further evaluated. Out-of-hours surgery for acute cholecystitis is not associated with a higher risk of complications, but with a higher proportion of open procedures.

# LIST OF SCIENTIFIC PAPERS

I Gustafsson C, McNicholas A, Sondén A, Törngren S, Järnbert-Pettersson H, Lindelius A.

**Accuracy of surgeon-performed ultrasound in detecting gallstones – A validation study**

*World Journal of Surgery 2016; 40(7): 1688-1694*

II Gustafsson C, Lindelius A, Törngren S, Järnbert-Pettersson H, Sondén A.

**Surgeon-performed ultrasound in diagnosing acute cholecystitis and appendicitis**

*World Journal of Surgery 2018; 42(11): 3551-3559*

III Gustafsson C, Dahlberg M, Lindelius A, Jervaeus E, Järnbert-Pettersson H, Sondén A.

**Repeated ultrasonography in acute cholecystitis**

*Submitted manuscript*

IV Gustafsson C, Dahlberg M, Sondén A, Järnbert-Pettersson H, Sandblom G.

**Is out-of-hours cholecystectomy in acute cholecystitis associated with complications?**

*British Journal of Surgery 2020; Published Online 26 April*

*(Wiley Online Library (www.bjs.co.uk). DOI: 10.1002/bjs.11633)*

# CONTENTS

# LIST OF ABBREVIATIONS

| | |
|---|---|
| ASA | American Society of Anaesthesiologists |
| ATLS | Advanced Trauma Life Support |
| BMI | Body mass index |
| CBD | Common bile duct |
| CI | Confidence interval |
| CRP | C- reactive protein |
| CT | Computed tomography |
| CVS | Critical view of Safety |
| ED | Emergency Department |
| FAST | Focused Assessment with Sonography in Trauma |
| IOC | Intraoperative cholangiography |
| LR | Likelihood ratio |
| MRI | Magnetic resonance imaging |
| NPV | Negative predictive value |
| NSAID | Non-steroidal anti-inflammatory drug |
| OR | Odds ratio |
| p | Probability, *p*-value |
| POCUS | Point of care ultrasound |
| PPV | Positive predictive value |
| RLQ | Right lower quadrant |
| RPUS | Radiologist-performed ultrasound |
| RUQ | Right upper quadrant |
| SPUS | Surgeon-performed ultrasound |
| TG | Tokyo Guidelines |
| US | Ultrasound/ ultrasonography |
| WBC | White blood cell |

# Introduction/summary

Symptomatic gallstones represent one of the most common reasons for patients presenting to the Emergency Department with acute abdominal pain[1]. The most common complication to gallstones is acute cholecystitis, *i.e.* inflammation of the gallbladder. To identify gallstones and to diagnose acute cholecystitis, ultrasound is the gold standard method. Today, the treating clinician may perform the ultrasound examination at the patient's bedside. Bedside, or point-of-care ultrasound (POCUS), performed by the surgeon, can save time for surgeons evaluating patients with suspected symptomatic gallstones and acute cholecystitis. However, large validation studies regarding the accuracy and reliability of such examinations are lacking.

Papers I and II were performed to validate surgeon-performed ultrasound for common surgical diagnoses: gallstones, acute cholecystitis and appendicitis. In Paper I, we found that surgeon-performed ultrasound was reliable in finding gallstones with an accuracy of 94.4%, and reached a high level of agreement to radiologists with Cohen's kappa 0.88. Paper II concerns diagnosing acute cholecystitis and appendicitis with ultrasound, which was shown to be more challenging. However, the accuracy for surgeon-performed ultrasound in these diagnoses were 93.9% and 77.3% respectively, and our results suggest that surgeon-performed ultrasound could be used to confirm, but not to rule out these diagnoses.

Patients suffering from recurrent episodes of biliary colic or acute cholecystitis may be considered for cholecystectomy. Papers III and IV concern acute cholecystitis: the role of ultrasound in this disease, prediction of difficult surgery, and the role of out-of-hours cholecystectomy. For patients with acute cholecystitis, the timing of surgery, in relation to the severity of the inflammation is important. The ability to predict a difficult cholecystectomy, with its attendant increase in risk of complications, is one of the main clinical problems facing the general surgeon. Currently, duration of symptoms is one of the main parameters used in such predictions[2-5]. The reviewed literature supports surgery within 72 hours from admission, or within five to seven days from onset of symptoms[6]. However, there are no widely accepted recommendations concerning the time-period immediately after the first 72 hours. Some patients might still benefit from same-admission surgery, while others may be better served by a delayed procedure in an elective setting, due to the potential technical difficulties during surgery with incipient scaring, fibrosis, and hyper-vascularisation associated with inflammation. The delayed procedure is intended to take place when the inflammation has subsided.

Patients with acute cholecystitis will differ in severity of symptoms, in severity of inflammation, and intraoperative complexity during cholecystectomy. Given the same duration from the onset of symptoms to cholecystectomy, one patient may be well suited for surgery while another may be at an increased risk of complications. Therefore, we believe that there is a need for more scientific evidence to support decision-making in the management of these patients. Specifically, it would be of importance to identify factors other than time, to discriminate between patients who would benefit from early cholecystectomy *versus* those with a higher risk of complications who would be better served by a delayed procedure. It would also be clinically important to identify risk factors for increasing intraoperative complexity, some of which may be possible to identify in preoperative ultrasound. In Paper III we attempted to describe the natural course of acute cholecystitis by performing repeated ultrasound examinations (once daily) in admitted patients. We found that the gallbladder wall thickness, as well as the gallbladder volume, showed a small tendency to decrease over time. The presence of oedema in the gallbladder wall was stable. Common for patients with no oedema was a long history of symptoms. The descriptive nature of this study makes it mainly hypothesis generating. One hypothesis would be that presence of oedema, together with with timing of the ultrasound examination, could be added to existing risk-stratification of difficult surgery for acute cholecystitis.

Effort is made to avoid in-hospital delays for patients with acute cholecystitis awaiting surgery. Whether to perform cholecystectomies at all hours, seven days a week has come to be discussed in this context[7-9]. There is limited evidence regarding the outcome for patients that undergo surgery out of hours. The impact of any iatrogenic complication, possibly due to an exhausted or inexperienced surgeon on call, is high. A central vascular or biliary injury may have serious consequences for the patient, requiring complex reconstructive surgery, possibly causing life-long morbidity and a reduced life expectancy[10]. In Paper IV we looked at complications within 30 days for patients that underwent out-of-hours surgery compared to office-hours surgery. The adjusted odds ratio for any complication out of hours was 1.12 (95% CI 0.99-1.28), *i.e.* a non-significant difference was found.

The overall aim of this research project was to validate surgeon-performed abdominal ultrasound for common surgical conditions such as gallstones, acute cholecystitis, and appendicitis, and to identify factors associated with increased intraoperative complexity, to aid decision-making when emergent cholecystectomy should be performed, delayed or even avoided, to minimise the risk for complications.

# Background

## Gallstones

### Aetiology

The concentrated bile in the gallbladder can cause formation of gallstones (cholelithiasis). There are different types of stones, classified according to their appearance and biochemical composition (cholesterol, bilirubin, calcium, phosphate)[11]. The different types of stones, however, are of limited clinical value, since symptoms can occur regardless of type or class. Formation of gallstones is associated with female gender, pregnancy, obesity, rapid weight loss, and a family history of gallstones[12, 13].

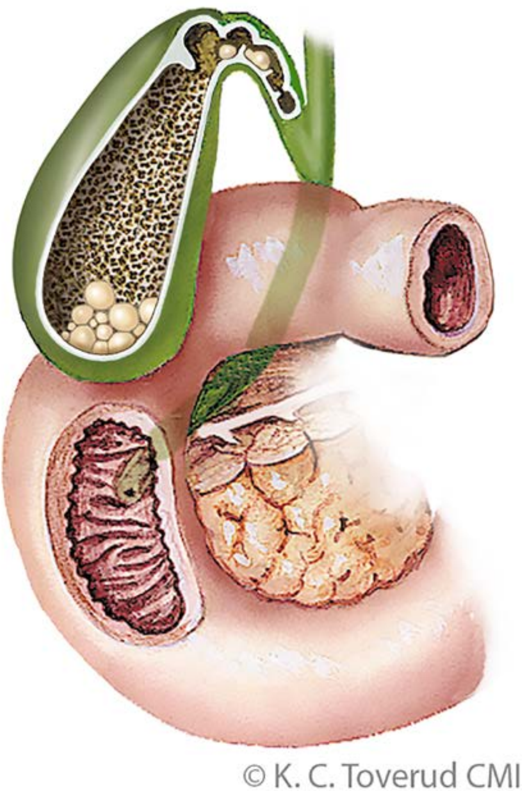


**Figure 1.** Gallbladder with stones, the common bile duct and pancreatic duct entering the duodenum.

## Uncomplicated gallstone disease

Symptomatic gallstone disease is one of the major causes of acute abdominal pain among adults. Around 10-15% of the overall adult population in the western world is believed to have gallstones[14-16], the incidence increasing with age. At the age of 60, around 30% of women and 20% of men have developed gallstones[17]. Most gallstones are asymptomatic with an annual incidence of developing symptoms around 1-4% among these individuals[12]. In screened populations, around 10% of individuals diagnosed with gallstones seem to develop symptoms within 5 years, and around 20% within 20 years[12, 16, 18].

### Clinical presentation

The symptoms from uncomplicated gallstone disease, recognised as biliary colic, rise from stones temporarily obstructing the cystic duct of the gallbladder, through which the bile is supposed to pass into the common bile duct (when emptying the gallbladder), and subsequently into the duodenum, as a response to food intake. Symptoms are abdominal pain, mostly situated in the right upper quadrant (RUQ) or epigastrium, often with radiating pain all over the upper abdomen, towards the back, and/or with referred pain to the right shoulder. Nausea and vomiting can be part of the clinical picture. Symptoms are typically described as postprandial, occurring within a couple of hours from a heavy meal, although they can occur at any time during the day. Duration is usually 15-30 minutes or slightly longer. When persisting pain for several hours is present, complicated gallstone disease should be suspected.

### Diagnosis

Ultrasound (US) is considered the gold standard for the diagnosis of gallstones[19, 20]. A review of the literature between 1966-1992, yielded a total sensitivity of 97% and a specificity of 95% for US in finding gallstones[21].

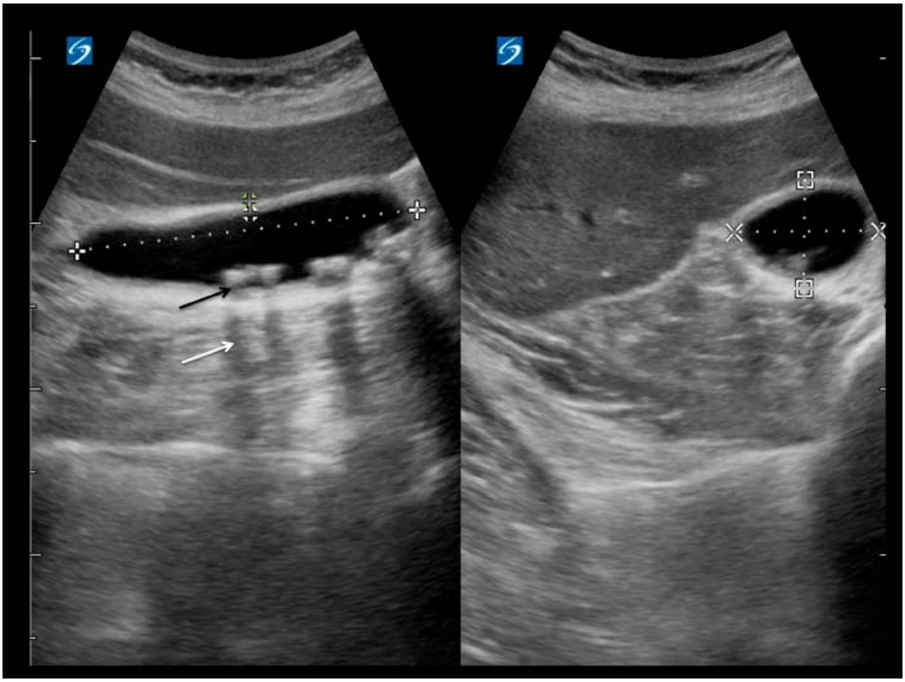

**Figure 2.** Ultrasound image of gallbladder with stones (black arrow) and concomitant stone-shadow (white arrow).

## Treatment

Asymptomatic gallstone disease is considered harmless and does not require prophylactic surgery[12, 22]. For patients with uncomplicated biliary colic with mild symptoms, non-steroidal anti-inflammatory drugs (NSAIDs) are the first-line treatment[23]. The risk of developing secondary complications from the gallstones for these patients is not thought to be significantly higher than that seen in asymptomatic patients[18]. For patients with more frequent symptoms however, the risk of developing complications is believed to be higher[12]. The decision to perform surgery in a patient with repeated symptoms is preferably made as an agreement between the treating surgeon and the patient, including a pre-operative discussion regarding morbidity, convalescence, and risk of complications associated with the procedure.

## Complicated gallstone disease

Gallstones can, apart from biliary colic, give rise to common bile duct (CBD) stones, biliary pancreatitis, jaundice, cholangitis, acute- and chronic cholecystitis. They are also a rare cause of small bowel obstruction.

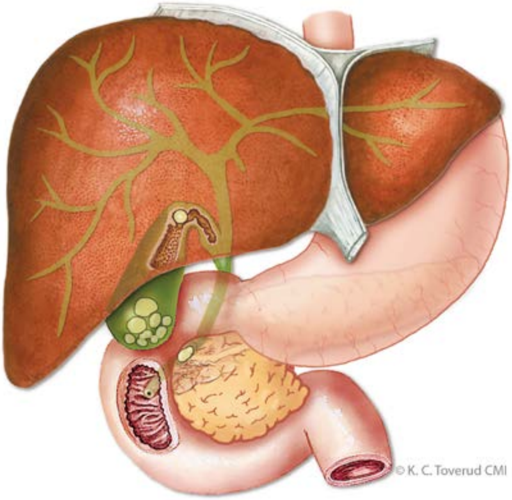


**Figure 3.** The liver with bile ducts. Gallbladder containing stones. Stomach, duodenum, and pancreas are also shown. A gallstone in the common bile duct is seen.

## Acute cholecystitis

### Aetiology

Acute cholecystitis, the most common complication to gallstones, affects around 20% of patients with symptomatic gallstones[24]. The development of acute cholecystitis is believed to result from a continuous obstruction of the cystic duct, usually by a gallstone, followed by distension and subsequent chemical or bacterial inflammation of the gallbladder[14, 25]. Around 90-95% of acute cholecystitis is believed to be calculous cholecystitis, *i.e.* caused by gallstones. Acute acalculous cholecystitis, inflammation of the gallbladder in the absence of gallstones, represents the remaining 5-10%. This is a condition typically found in critically ill patients, treated in an intensive care unit. The aetiology of this condition is physiologically unrelated to that of calculous cholecystitis and will not be discussed further in this thesis.

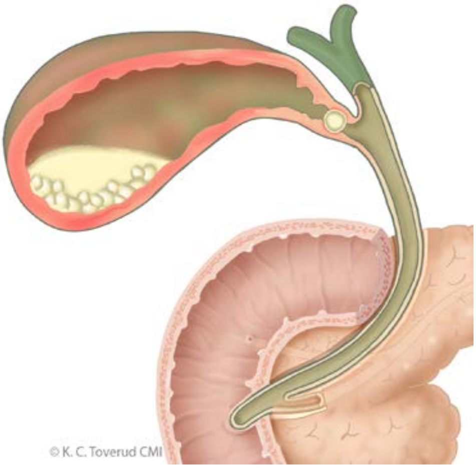


**Figure 4.** Inflamed gallbladder wall, due to obstruction of the cystic duct by an impacted stone.

### Clinical presentation

Similar to biliary colic, RUQ pain is the dominant symptom of acute cholecystitis. Persistent pain from hours to days with simultaneous fever, represent typical symptoms.

### Diagnosis

The diagnosis of acute cholecystitis is based on an overall assessment consisting of clinical, radiological, and laboratory findings.

## Tokyo Guidelines

Following a consensus meeting in 2007, the Tokyo Guidelines (TG) diagnostic criteria for acute cholecystitis and cholangitis were established[26]. The guidelines have been accepted and recognised as the recommendation for diagnosis of acute cholecystitis[24]. They have been adopted throughout the gastrointestinal surgical community and are regularly revised and updated[27, 28]. The TG13/18 diagnostic criteria for acute cholecystitis[29] are listed below:

A. Local signs of inflammation (positive Murphy's sign or RUQ mass/pain/tenderness)

B. Systemic signs of inflammation (fever, elevated C-reactive protein (CRP), and/or elevated white blood cell (WBC) count)

C. Imaging findings (characteristics of acute cholecystitis).

Suspected diagnosis: one from A + one from B

Definite diagnosis: one from A + one from B + C

Validation of these criteria shows a diagnostic accuracy ranging between 60.4%[30] and 94%[31].

The guidelines also include a severity grading classification[29], with three grades based on the clinical features and prognostic factors for the patient with acute cholecystitis. The severity grades include:

- I Mild. Acute cholecystitis in a healthy patient with no organ dysfunction, mild inflammatory changes of the gallbladder, and considered safe to perform cholecystectomy
- II Moderate acute cholecystitis. Associated with any of the following:
  1. Elevated WBC count > 18.000/mm$^3$
  2. Palpable tender mass in the RUQ
  3. Duration of symptoms > 72 hours
  4. Marked local inflammation (*e.g.* gangrenous or emphysematous cholecystitis, pericholecystic or intrahepatic abscess)
- III Severe acute cholecystitis. Associated with organ dysfunction in any of the following organ systems:
  1. Cardiovascular
  2. Neurological
  3. Respiratory
  4. Renal
  5. Hepatic
  6. Haematological

The severity grading guidelines are used as a base for treatment strategies, and have been validated in a number of studies[32-35]. In addition to TG, there have been several other scoring systems proposed for acute cholecystitis, focusing on severity grading and predicting difficult surgery[36-39]. Some have focused on the preoperative clinical and patient-dependent factors[36, 39], while others more on the intraoperative visualisation of inflammatory and anatomically changes[40, 41], or a combination of the two. The large number of scoring systems highlights the need for a simple, universally accepted method of predicting difficult surgery. However, the following parameters are generally accepted as preoperative indicators of complicated/ gangrenous acute cholecystitis: male gender, age >50 years, diabetes, elevated WBC count, and thickening of the gallbladder wall ≥ 4 mm[39, 42, 43].

### Gangrenous acute cholecystitis

The term gangrenous cholecystitis refers to the development of necrosis in the gallbladder wall, and occurs in 2-30% of cases with acute cholecystitis[14]. The gangrene is often found at the fundus of the gallbladder, as a result of decreased vascular supply to this area[14].

### Emphysematous acute cholecystitis

Secondary infection with gas-forming organisms in the gallbladder wall can cause emphysematous cholecystitis. This is a rare condition, but male patients between 50-70 years are overrepresented. Atherosclerosis and diabetes also seem to be risk factors[44]. Emphysematous cholecystitis can cause gangrene, perforation and formation of a pericholecystic abscess. It is not necessarily associated with gallstones[45].

## Natural course of acute cholecystitis

The natural course of acute cholecystitis is neither fully understood, nor described in the literature. There is a possibility that different types of inflammation exist, in analogy with the theory of acute appendicitis[46], with some cases rapidly developing gangrene. Although the time frame of development is not well defined, gangrenous cholecystitis is considered a risk factor for complicated disease, gallbladder perforation, and difficult surgery[42]. Another complicating factor is the difference in clinical presentation. While some patients seek emergency care with a relatively short history of on-going symptoms, other patients wait for several days[47]. This could be due to patient factors alone, or possibly to factors related to the disease. In any case, either of these factors could affect the outcome of surgery[47].

# Treatment

## Surgery

The treatment of acute cholecystitis and timing of cholecystectomy have been discussed and debated for at least a century. In an article published in the Annals of Surgery in 1938, conservative treatment was advocated, especially for severely ill patients and for patients with gangrenous cholecystitis, due to high perioperative mortality among the 300 studied patients with observation times of on average 8 days (maximum 23 days)[48]. The same author also pointed out that many treatment strategies follow a cycle in time: *"Methods of treatment change with time. There is frequently the same tendency to cycles which is so characteristic of all human activities and customs"*[48]. A cursory examination of the literature shows that treatment strategies for acute cholecystitis have indeed changed a few times during the 20th century. Currently, surgical treatment with cholecystectomy is the preferred treatment of choice, according to current gudelines[29], despite the lack of evidence supporting its superiority over conservative treatment. Prospective and randomized controlled studies on this issue are lacking[49].

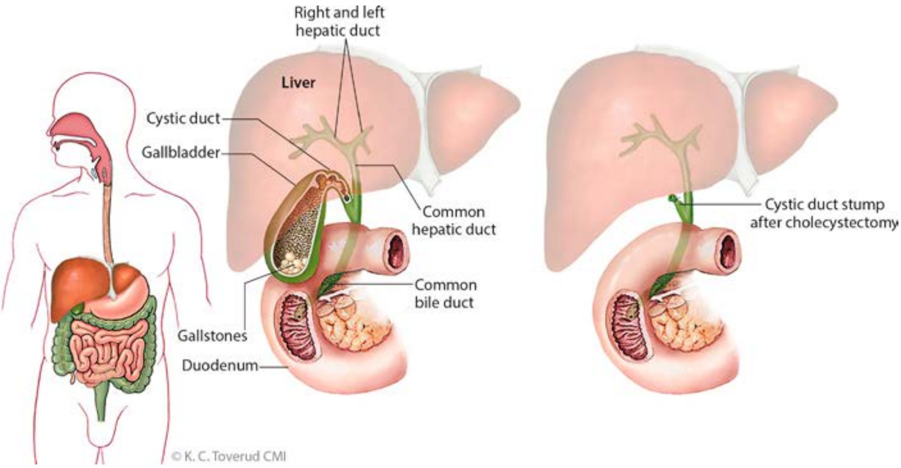


**Figure 5.** Anatomy before and after cholecystectomy

## History of cholecystectomy

The first cholecystectomy was performed by Langenbuch, in Berlin 1882, and the first laparoscopic cholecystectomy was performed by another German surgeon, Mühe, around one hundred years later (1985), although he was neither given credit, nor much attention for this, at the time[50]. The first laparoscopic cholecystectomy to be publicly acknowledged was performed two years later by the Frenchman Mouret, in Lyon, France[50]. He used a video-laparoscope and the four-trocar technique, similar to the technique in use today. The development of the laparoscopic procedure accelerated during the 1990's. Initially, the procedure was associated with a higher risk of complications compared with open cholecystectomy, especially bile duct injuries (BDI)[51-53]. The reduction in morbidity, length of stay, and hospital costs associated with the laparoscopic procedure compared to open surgery, however, served as a strong incentive to adopt the method despite a somewhat increased risk of complications at the start of the learning curve. With the increased use and development of the procedure, there was a subsequent improvement in outcomes[54, 55], Today, the incidence of BDI in laparoscopic cholecystectomy is around 0.2%[56], which is in the same range as that reported for open surgery[51], and laparoscopic cholecystectomy is one of the most common surgical procedures performed in the Western world[57].

## Timing of surgery

Current guidelines recommend early surgery after hospital admission[2, 6, 58-60]. In the newly updated Tokyo Guidelines (TG18), early laparoscopic cholecystectomy for acute cholecystitis is recommended regardless of the grade of severity, and a delayed procedure (six to eight weeks later) should only be chosen in selected high-risk cases[29, 61]. Although early cholecystectomy is widely recognised as the preferred approach, as discussed above, in clinical practice there is often an in-hospital delay until the procedure is performed, due to prioritisation of more urgent cases.

In a large review of 4113 laparoscopic cholecystectomies in patients with acute cholecystitis, published in 2011, higher conversion rates and longer operative times were seen for each day from admission that surgery was delayed[3]. It is believed that surgery should be performed before the start of fibrosis formation in the gallbladder tissue[61], although the exact time frame for this process has not been elucidated. Furthermore, there is no consensus on the definition of "early surgery". Another large retrospective study from 2015 (including 95.523 patients), concluded that patients benefit from surgery within 48 hours from admission[5]. Several studies promote surgery within the first 24-72 hours[2, 3, 59, 60, 62, 63], while others have concluded it safe, with respect to complications, to proceed with same-admission surgery within the first seven days from onset of symptoms[64, 65]. A Cochrane review from 2013, concluded that there was no difference in complications between early and delayed surgery – but that early surgery (up to seven days from onset) was associated with a total shorter length of stay and socio-economic benefits due to earlier return to work[58].

## Difficult surgery

When the anatomy around the gallbladder is altered due to inflammation, surgery can be challenging. Minimising perioperative complications, especially biliary or vascular damage is of utmost importance. The risk and incidence of complications may be reduced if predictors of difficult surgery were identified. In addition to the preoperative scoring systems previously mentioned, repeated intraoperative evaluation by the surgeon during the procedure is important. In effort to reduce the increased risk of bile duct injuries in the beginning of the laparoscopic era, an attempt was made to provide safe steps in the laparoscopic procedure, when in 1995 the "Critical view of Safety" was first introduced by Strasberg[66].

## Critical view of Safety

Using the critical view of safety (CVS) technique implies that the anatomy should be adequately perceived before the division of any vital structures. The triangle of Calot (bordered by the cystic duct, the cystic artery and the common hepatic duct) should be visualised, and the only two structures entering the gallbladder should be identified as the cystic duct and artery. The dissection of the lower one third of the gallbladder (from the gallbladder neck and upwards) from the cystic plate (often referred to as the gallbladder bed of the liver) enables this.

To perform surgery systematically in safe steps is valid for all cases of chole-cystectomies, whether referred to as the CVS technique or not. It is of particular importance to be careful in case of acute cholecystitis when the anatomy could be altered, and difficult to interpret, due to the inflammatory changes.

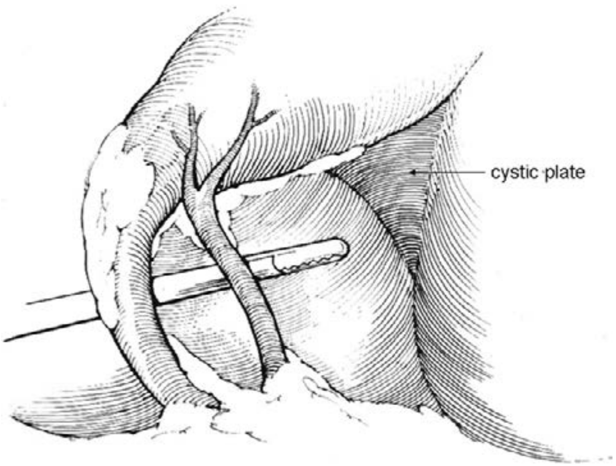


**Figure 6.** The critical view of safety. Dissection of the "lower part" of the gallbladder from the cystic plate gives rise to two tubular structures leading towards the gallbladder. (Reprinted from Journal of American College of Surgeons[66], with permission from Elsevier)

## Intraoperative cholangiography

The use of intraoperative cholangiography (IOC), which is routinely performed during cholecystectomy in Sweden[67], may aid correct interpretation of the anatomy around the gallbladder. The intention to use IOC has been shown to reduce the frequency of bile duct injuries in patients with acute cholecystitis[53, 67-70]. It provides early detection of any iatrogenic bile duct injury and can improve survival in patients who suffer this complication[10, 71]. IOC can also reveal the presence of CBD stones, which is present in approximately 15% of cases with acute cholecystitis[72]. However, intraoperative cholangiography has not been adopted globally as a standard procedure in laparoscopic cholecystectomy.

## Out-of-hours surgery

One way to avoid the delay of surgery for patients with acute cholecystitis is to perform laparoscopic cholecystectomy also out of hours. In some countries acute care surgery models have been developed, in order to improve the timeliness of care[73-75]. The matter of performing laparoscopic cholecystectomy 24 hours a day, seven days a week has been discussed, as it is not clear whether surgery undertaken out of hours affects the risk of complications and other patient outcomes[7-9, 76]. In a systematic review from 2014, Nagaraja *et al.* found a shorter hospital stay, as well as a lower complication rate after acute cholecystectomy, when an acute care surgery model was followed[75]. A decrease in night-time (out-of-hours) surgery and a reduction in the actual waiting time from the emergency department to the operating room was seen[73, 75]. Data on the safety of out-of-hours laparoscopic cholecystectomies are somewhat conflicting and relevant studies are sparse. A large retrospective study by Gabriel *et al.* in 2018, showed no difference between daytime and out-of-hours surgery in peri-operative mortality for emergent general surgery cases[77]. Studies that have specifically focused on night-time laparoscopic cholecystectomy for acute cholecystitis include Phatak *et al.* (2014), who performed a single-centre retrospective study of 356 non-elective laparoscopic cholecystectomies. The authors found that night-time surgery for acute cholecystitis was associated with a small increase in the risk of complications, largely due to an increase in the incidence of surgical site infections and retained stones, but also with a shorter length of stay[7]. In contrast Wu *et al.* (2014) retrospectively reviewed 1140 patients at two large surgical units and found that night-time laparoscopic cholecystectomy was associated with a higher risk of conversion to open surgery, and that there was no decrease in length of stay, thus advocating surgery to be postponed to the morning[76]. Siada *et al.* (2017), on the other hand, showed in a similarly designed study with 866 comparable patients, a decrease in length of stay, (although only marginally – from 2.8 to 2.4 days) when comparing daytime to night-time surgery, along with no significant difference in complications between the two groups, and concluded it safe to perform out-of-hours laparoscopic cholecystectomy[8]. However, serious complications such as bile duct injuries are rare (around 0.2%) and none of these studies had sufficient power to assess this[56]. Hence, the impact on outcome of out-of-hours surgery for acute cholecystitis is still not clear.

### Antibiotics

The inflammation of the gallbladder wall seen in acute cholecystitis is thought to be chemical, rather than caused by bacterial infection[14]. Nevertheless, international recommendations include antibiotics as first-line treatment for acute cholecystitis, even if the role of bacteria at early stages of the disease is questioned[78]. In Sweden, however, routines regarding antibiotics differ from these recommendations, and decisions regarding antibiotic treatment are rather made on an individual basis. Generally, patients with signs of bacterial infection, such as fever (temperature above 38°C) or suspected development of sepsis are given antibiotics. The belief is that the early, non-bacterial inflammation does not require antibiotic treatment, but that the obstructed gallbladder may later be colonised by bacteria from the intestinal flora, which can lead to bacterial infection. The rationale behind a stricter, more limited use of antibiotics is to try to prevent, or at least reduce, the development of antimicrobial resistance[79]. In general, acute cholecystitis of Tokyo severity grade II would probably result in antibiotic treatment also in Sweden. For this group, Piperacillin/Tazobactam is the recommended drug, in line with international recommendations[78].

### Cholecystostomy

For high-risk patients (*e.g.* the elderly or patients with extensive comorbidity), the role of percutaneous biliary drainage, cholecystostomy, has been repeatedly discussed as an alternative to cholecystectomy or as bridge to surgery. According to TG18[6], cholecystostomy is recommended for patients unfit for surgery with uncontrolled inflammation of the gallbladder, although there is currently no strong evidence regarding its benefits[80, 81]. An on-going randomized controlled trial in the Netherlands, comparing cholecystostomy to acute cholecystectomy in high-risk patients, may possibly improve the evidence base when concluded and reported[82].

## Imaging in acute cholecystitis

Different modalities for imaging acute cholecystitis were compared in a 2012 systematic review and meta-analysis[83]. It showed that cholescintigraphy was the most sensitive and accurate modality for demonstrating acute cholecystitis. The sensitivity and specificity of US and magnetic resonance imaging (MRI) were similar, while computed tomography (CT) scan was considered under-evaluated, due to lack of relevant studies[83]. These results were similar to a previous systematic review performed by Shea *et al.* in 1994[21].

## Ultrasonography – Gold standard

Ultrasonography is considered the gold standard imaging method in diagnosing acute cholecystitis[29]. The low invasiveness of ultrasonography, together with high availability, low cost, and relatively accurate examinations[21, 83], has made it the first-choice imaging technique for examining this group of patients[29].

The sensitivity has been reported as 81-88%[21, 83]. Diagnostic features suggestive of acute cholecystitis include a distended gallbladder and gallbladder wall thickening of more than 3-4 mm[84]. Pericholecystic fluid may be present. The ability to elicit the sonographic Murphy's sign (tenderness when the examiner places the probe directly over the gallbladder) is a clinical advantage with this modality, as the sign in itself has a high accuracy for the diagnosis[84].

## Computed tomography (CT)

A CT scan is unable to detect non-calcified gallstones. The sensitivity in diagnosing acute cholecystitis has been reported to be between 73-85%[85, 86]. The modality has the advantages of being accessible, rapidly performed, non-operator dependent, and to provide answers to possible differential diagnoses, especially in the elderly or in patients with diffuse abdominal pain. It is also a good modality to diagnose complications of acute cholecystitis, such as perforation or abscess formation[87].

## Magnetic Resonance Imaging (MRI)

The sensitivity of MRI in demonstrating acute cholecystitis has been shown to be similar to that of US, or slightly higher (85-86%)[83], but the lack of availability along with an increase in examination times and costs have made the method less clinically useful than US. However, current guidelines recommend the use of MRI if US cannot provide a definite diagnosis, due to the slightly higher accuracy[29].

## $Tc^{99m}$-labeled hepatobiliary iminodiacetic acid (HIDA) scan

Cholescintigraphy, or HIDA scan, provides the highest accuracy in diagnosing acute cholecystitis, with a sensitivity of 96% and a specificity of 90%[83]. The sign of cholecystitis is non-visualisation of the gallbladder on the scintigram, due to obstruction of the cystic duct[88]. The method is less sensitive in diagnosing the complications from and/or differential diagnoses to acute cholecystitis and the availability is generally low[89].

## Point-of-care ultrasound

Radiologist-performed US (RPUS) is not always accessible in the emergency department (ED), especially out of hours. This can lead to unnecessary delay in patient management[90]. Consequently, non-radiologist-performed US, or point-of-care US (POCUS), used at the patient's bedside has increased during the last decades[91, 92]. Cardiologists and obstetricians have a long experience of using US in their clinical practice, but the development of portable, affordable, and user-friendly machines has laid ground for wider use in other specialties. Today emergency medicine physicians, anaesthetists, as well as surgeons use US as a diagnostic tool[92, 93].

### Surgeon-performed ultrasound (SPUS) = POCUS by surgeons

A wide range of uses of surgeon-performed US has been reported, including in traumatic conditions, diagnostic, and interventional procedures. In the acute care setting, focused assessment with sonography in trauma (FAST) has changed the management of trauma patients, now being integrated in the concept of advanced trauma life support (ATLS), and represents one of the earliest, most basic forms of SPUS. Diagnostic use of US by surgeons includes examinations of the breast, thyroid gland, vascular system, and the gastrointestinal tract[91]. SPUS has been shown to help surgeons in their decision-making regarding patients with abdominal pain in the ED[94, 95]. In a newly published article from a 2018 consensus meeting in Valencia, Spain, recommendations for extended use of surgeon-performed POCUS, (*e.g.* as first-line examination in suspected acute cholecystitis) was presented[96]. However, there is still lack of evidence regarding validation of POCUS examinations.

### Accuracy of surgeon-performed ultrasound

Some previous studies have shown a high sensitivity as well as accuracy of SPUS in biliary tract disease, but few have large patient samples[90, 97-99]. In a systematic review from 2013, Carroll *et al.* pooled the numbers from several studies evaluating surgeon-performed US of the right upper quadrant (RUQ)[100]. There was significant heterogeneity among existing validation studies regarding inclusion criteria, diagnostic criteria, definition of reference standard, number of participating surgeons, and level of experience in ultrasonography. Diagnostic criteria in the included studies ranged from the presence of gallstones or cholecystitis to any biliary tract disease, the latter often without further specification. Nevertheless, the pooled results suggested that surgeons become clinically capable of performing a RUQ scan after a short education in US (ranging between 1 hour and 5 days). It seems that the number of supervised examinations needed to perform reasonably valid gallbladder ultrasound examinations, for gallstone detection, is somewhere around 25[101]. In 2012, Shepherd *et al.* called out for consensus regarding the training of

POCUS for surgeons, in an attempt to address the need for standardisation. There is a need for collaboration between general surgeons, radiologists and educators to establish internationally valid guidelines and in the end to achieve an accreditation system[102].

**Figure 7.** Surgeon in US training at Södersjukhuset, Stockholm.

Since 2004, Stockholm South General Hospital (Södersjukhuset) provides a training programme in abdominal US for surgeons. The programme is a collaboration between the Surgical and Radiology Departments. Ultrasound-experienced surgeons, together with radiologists and sonographers have provided US training for surgical trainees. In a randomized controlled clinical trial, conducted at the same hospital, with 800 randomized patients, Lindelius *et al.* showed in 2008 that US-trained surgeons reached a higher level of overall diagnostic accuracy in the ED, when using US as a part of their clinical examination, compared with when not using US[103]. A question that remained unanswered was how accurate the surgeon-performed US examinations were. It has been demonstrated that surgeons can detect gallstones with a high diagnostic accuracy, using US[90, 95, 97, 98]. Previous work on the diagnostic accuracy of radiologist-performed US in acute cholecystitis and appendicitis has shown variable results. The reported sensitivity differs, ranging from 50-88% for acute cholecystitis[21, 83, 85, 104, 105] and 52-76% for appendicitis[85, 106]. The quality of abdominal US in these contexts appears to be operator-dependent, which may have a negative impact on the quality of SPUS, since surgeons may not receive the same amount of US training as radiologists[101]. To what extent this matters, however, is not known, since studies on the subject are few[107].

# Fields to explore

Although a lot of time and effort have been put into research on acute cholecystitis, knowledge is still lacking regarding the natural course of the disease. There is a possibility that different types of inflammation exist, based on different triggering mechanisms and different patient characteristics, thereby leading to differing patient outcomes.

There is a need for a universal preoperative risk-scoring system for prediction of difficult surgery in acute cholecystitis, to help evaluate patients more reliably.

Previous work correlating ultrasonographic findings to severity of disease, operative difficulty, or postoperative complications have linked increased thickness of the gallbladder wall with increasing severity grade of acute cholecystitis[36, 39, 108-111]. However, these studies have been based on performing a single US examination at a poorly defined time-point. Systematic follow-up from time of admission or diagnosis, with repeated US examinations focusing on gallbladder parameters, has not been reported for patients with acute cholecystitis. Small case series of repeated US examinations in the emergency department have shown rapid development of marked changes in the gallbladder wall thickness (up to 3-4 mm thickening in 1-4 hours)[112, 113]. Although it is difficult to draw robust conclusions from this, these studies reveal a gap in the knowledge regarding the timespan and ultrasonographic features during the development of acute cholecystitis. It is therefore possible that following the evolution of gallbladder morphology with US during acute cholecystitis could improve our understanding of the course of the disease and help predict intraoperative complexity.

As POCUS has become widely adopted worldwide, there is a need for further validation of these US examinations.

# Aims and Hypotheses

The overall aim of this thesis was to optimise the treatment and timing of surgery for patients with acute cholecystitis, and to evaluate the role of ultrasound in risk scoring these patients.

The specific aims were:

- To validate surgeon-performed ultrasound for common surgical diagnoses (gallstones, cholecystitis and appendicitis).

Hypothesis: Surgeons can reach high accuracy and a good level of agreement to radiologists in these basic examinations. ***(Papers I and II)***

- To explore and describe potential ultrasonographic changes of the gallbladder, in patients with on-going acute cholecystitis, by performing repeated ultrasonography.

Hypothesis: If typical changes are visible with ultrasound over time, this could play a further role in preoperative risk estimation, and support decision-making regarding surgery. ***(Paper III)***

- To study if out-of-hours surgery is associated with an increased risk of complications for patients with acute cholecystitis.

Hypothesis: Out-of-hours laparoscopic cholecystectomy is associated with a higher risk of complications compared with office-hours surgery. ***(Paper IV)***

# Patients and Methods

| Paper | I | II | III | IV |
|---|---|---|---|---|
| Research question | Validity of SPUS in diagnosing gallstones? | Validity of SPUS in diagnosing cholecystitis and appendicitis? | Sonographical natural course of acute cholecystitis? | Is out-of-hours cholecystectomy associated with complications? |
| Study design | Clinical cohort | Clinical cohort | Clinical cohort | Register-based cohort |
| Data sources | Study protocol | Study protocol, patient charts | Study protocol | Swedish National Register for gallstone surgery (GallRiks) |
| Inclusion criteria | RUQ scan, Informed consent | RUQ or RLQ scan, Informed consent | Acute cholecystitis (TG13) Informed consent | Acute cholecystitis, acute surgery, time of day registered |
| Exclusion criteria | Age < 18 years, inability to communicate | Age < 18 years, inability to communicate | Age < 18 years, inability to communicate | Elective procedures, no registration of time of day |
| Time period | 2011-2012 | 2011-2012 | 2017-2018 | 2006-2017 |
| Number of patients | 179 | 164/44 | 88 | 11 153 |
| Exposures | Abdominal ultrasound | Abdominal ultrasound | Abdominal ultrasound | Out-of-hours surgery |
| Outcomes | Presence of gallstones | Presence of acute cholecystitis or appendicitis | Changes in gallbladder wall thickness, gallbladder volume | Complications, Open surgery, Operative time ≥ 2hrs |
| Statistical analyses | Sensitivity, Specificity, PPV, NPV, Accuracy, Kappa Index | Sensitivity, Specificity, PPV, NPV, Accuracy, Likelihood ratio, Kappa Index | Fisher's exact test, Mann Whitney U test | Logistic regression, Classification tree |

Brief overview of papers included in the thesis

## Study design and data sources

Study I, II and III were clinical prospective studies, with data collection from study protocols. Study IV was a register-based cohort study where data were collected from the Swedish National Register for gallstone surgery and ERCP procedures, GallRiks. The register was founded in 2005 and covers more than 90% of all gallstone procedures in Sweden[114]. Around 12 000 cholecystectomies and 8000 ERCP procedures are registered in GallRiks each year. The register has been validated and a high completeness, as well as correctness (around 97%) has been reported[115].

## Study population

Patients referred to the radiology department at Stockholm South General Hospital, for any diagnostic abdominal US examination, were enrolled between October 2011 and November 2012. This cohort was used for analyses in Paper I and Paper II.

Paper III consists of patients with acute cholecystitis admitted to the surgical department at the same hospital, between October 2017 and October 2018.

In Paper IV, patients that underwent surgery for on-going acute cholecystitis and were registered in GallRiks between 2006 and 2017 were included.

## Inclusion criteria

In Paper I, all patients that received a RUQ scan from both the surgeon and radiologist, with respect to gallstones, were included. In Paper II, patients with suspected biliary disease and/or suspected appendicitis were included. Suspected biliary disease was defined as patients presenting with pain in the right upper quadrant (RUQ) and/or tenderness in the RUQ during physical examination and/or with a referral to the radiology department regarding gallstones and/or cholecystitis. Suspected appendicitis was defined as patients presenting with pain in the right lower quadrant (RLQ) and/or tenderness in the RLQ and/or with a referral to the radiology department regarding appendicitis.

In Paper III, all patients with a first episode of acute cholecystitis, diagnosed according to TG, admitted to the surgical department were eligible.

All patients gave written consent for participating in the clinical studies (I-III).

In Paper IV, the inclusion criteria were surgery for acute cholecystitis and a valid registration of time of day (when surgery was commenced), reported in GallRiks.

## Sample size

A sample size of 190 patients was the result of a power calculation for Paper I, designed to detect a difference between SPUS and RPUS in diagnosing gallstones. This is further described in the section of statistical analyses.

In consultation with the hospital's radiology department, it was estimated that two thirds of all patients being referred to the radiology department for an abdominal scan would be examined for the occurrence of gallstones. Enrolment was therefore aimed at 300 patients in pursuit of 190 included patients with a RUQ scan. The same cohort was then used in Paper II to evaluate the additional diagnoses acute cholecystitis and appendicitis. In Paper I, 179 patients were finally included. In Paper II, the numbers were 164 patients examined for acute cholecystitis, and 44 patients examined for appendicitis.

In Paper III, the aim was to include all patients with a confirmed diagnosis of acute cholecystitis, and it was estimated that between 200-300 patients are admitted to the hospital due to this diagnosis every year. Out of 120 patients, who were initially examined with ultrasound for suspected acute cholecystitis, 88 patients were eventually included.

In Paper IV, all patients registered in GallRiks (between 2006 and 2017) as non-elective cholecystectomy for acute cholecystitis, with a noted time of day of the procedure, were included, which yielded 11 153 patients.

## Exposure

In Papers I and II, included patients received one US examination by the surgeon as well as a standard US examination by the radiologist. The surgeon and radiologist were blinded to the findings of each other. Examinations were done immediately after one another when possible, and always within an interval of less than six hours.

In Paper III, patients received repeated US examinations by a sonographer or a radiologist.

In Paper IV, the exposure was surgery performed out of hours. If the procedure was initiated between 19.00 and 07.00 on weekdays, or at any time during the weekend (from Friday 19.00 until Monday 07.00), it was considered a procedure performed out of hours.

## Outcome

In Papers I and II, the outcome was diagnosis stated by the surgeon. Radiologist-performed US was used as reference (gold standard) in Paper I. In Paper II, final diagnosis on discharge was used as reference.

In Paper III, which was mainly descriptive, the outcome was any change in gallbladder parameters, such as gallbladder volume, gallbladder wall thickness, and the presence/development of oedema in the gallbladder wall.

In Paper IV, the primary outcome was any complication to surgery within 30 days. Secondary outcomes were surgery completed as an open procedure and operating time exceeding two hours.

## Statistical analyses

McNemar's test of paired proportions was used to detect a systematic difference in detecting gallstones between the surgeon and the radiologist, postulated as 2% *versus* 8% (gallstones identified only by the surgeon, *versus* only by the radiologist). This was estimated to be the smallest clinically relevant difference. A sample size of 190 patients being scanned for gallstones was calculated using SamplePower 2.0 and was set to detect this difference with a power of 80%. A $p$-value <0.05 (two tailed) was considered statistically significant. Sensitivity, specificity, overall accuracy, positive predictive value (PPV), and negative predictive value (NPV) for SPUS were analysed in both Papers I and II. In addition to this, the positive and negative likelihood ratios ($LR^+$ and $LR^-$) for SPUS and RPUS in detecting gallstones, cholecystitis and appendicitis were calculated in Paper II. The inter-observer agreement between surgeons and radiologists was calculated for each of the three diagnoses using Cohen's kappa.

The study was registered at Clinical Trials (clinicaltrials.gov identifier NCT02469935).

In Paper III, comparisons between patients with single and multiple ultrasound examinations were done with Fisher's exact test (categorical parameters) or Mann-Whitney U-tests (continuous non-parametric variables), to see whether the group that received multiple examinations differed significantly from patients receiving one examination. Two-sided $p$-values less than 0.05 were regarded significant.

The study was registered at Clinical Trials (clinicaltrials.gov identifier NCT03470220).

In Paper IV, out-of-hours surgery was compared with office-hours surgery for acute cholecystitis, using univariable and multivariable logistic regression analyses. Odds ratios (OR) were reported with 95% confidence intervals (CI), and a two-tailed test with a *p*-value of less than 0.05 was considered significant. We also used classification tree analysis to identify exposure variables associated with complications, and to identify groups of patients with different risks (proportions) of complications. The Chi square Automatic Interaction Detection (CHAID) algorithm was used to construct the tree[116].

To study a possible association between time of day and the outcomes any complication and open surgery, these outcomes were also modelled in separate logistic regression analyses, adjusted for sex, age and ASA-score. A continuous time model for weekday data was used to visualise the variation of the outcomes, depending on the time of day when surgery began, with restricted cubic splines for the variables time of day and age.

## Ethical considerations

All studies (I-IV), were approved by the Regional Ethical Review Board in Stockholm.

# Results

## Paper I

Of the 300 patients enrolled, 179 received a scan of the RUQ, including the gallbladder, from both a radiologist and a surgeon. Surgeon-performed US was in agreement with radiologist-performed US in 169 of 179 patients, reaching an overall accuracy of 94.4% (95% CI: 90.0-96.9%). The sensitivity was 88.2% (79.0-93.6%) and the specificity was 99.0% (94.7-99.8%). The inter-observer agreement between surgeons and radiologists was high for the detection of gallstones, with a Cohen's Kappa coefficient (kappa index) of 0.88.

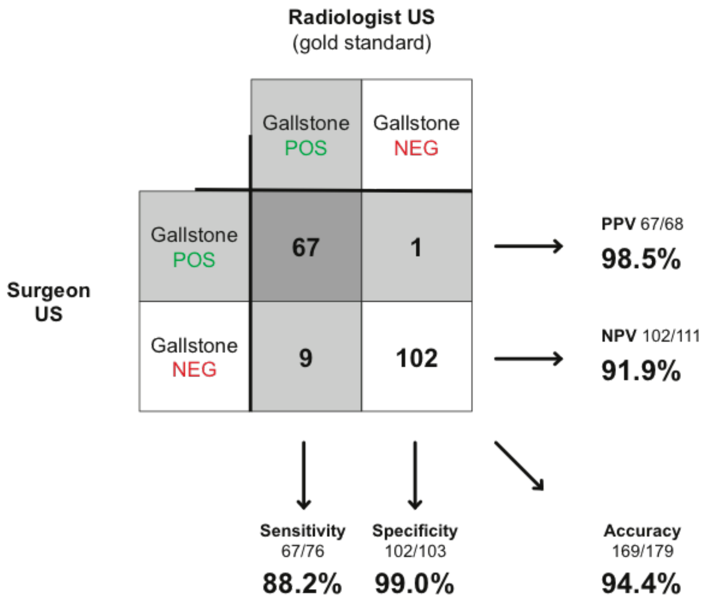


**Figure 8.** SPUS in diagnosing gallstones

The overall prevalence of gallstones in this cohort was 42.5% (76/179).

Outside the scope of Paper I, but extracted from the data, are the individual results of each study surgeon participating in the study. Each surgeon performed a different number of examinations with respect to gallstones (range 16-49), which is visualised in *Figure 9*, with the proportion of accurate scans presented.

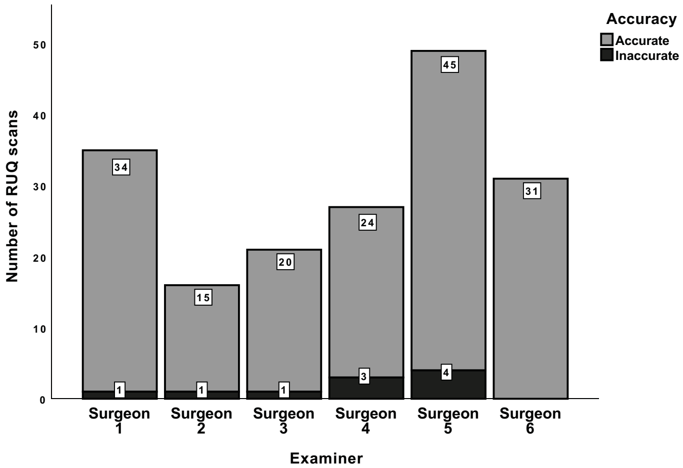


**Figure 9.** Number of scans (accurate and inaccurate) performed by each study surgeon

The results reflect the observer dependent nature of ultrasound examinations. Individual interobserver agreements between each surgeon and radiologist were calculated:

Surgeon 1 (35 examinations): Kappa index = 0.94

Surgeon 2 (16 examinations): Kappa index = 0.88

Surgeon 3 (21 examinations): Kappa index = 0.91

Surgeon 4 (27 examinations): Kappa index = 0.74

Surgeon 5 (49 examinations): Kappa index = 0.82

Surgeon 6 (31 examinations): Kappa index = 1.0

To better understand the interpretation of Cohen's kappa, reference values are listed in *Figure 10*.

| Interpretation of interobserver agreement using Cohen’s Kappa index | |
|---|---|
| < 0 | Less than chance agreement |
| 0.01 – 0.20 | Slight agreement |
| 0.21 – 0.40 | Fair agreement |
| 0.41 – 0.60 | Moderate agreement |
| 0.61 – 0.80 | Good agreement |
| 0.81 – 0.99 | Very good agreement |
| 1.0 | Perfect agreement |

**Figure 10.** Interobserver agreement

## Paper II

In Paper II, the accuracy of surgeon-performed ultrasound in diagnosing acute cholecystitis and appendicitis was evaluated. Radiologist-performed US was also evaluated for both acute cholecystitis and appendicitis, for comparative reasons.

The sensitivity for SPUS in diagnosing acute cholecystitis was 60.0%, the specificity was 98.6% and the overall accuracy was 93.9%, as shown in *Figure 11*.

The positive and negative likelihood ratios ($LR^+$ and $LR^-$) are also shown. The likelihood ratio shows how much more likely someone with the disease is to get the test result compared with someone without the disease to get the test result. A $LR^+$ of 43 and $LR^-$ of 0.41 were found.

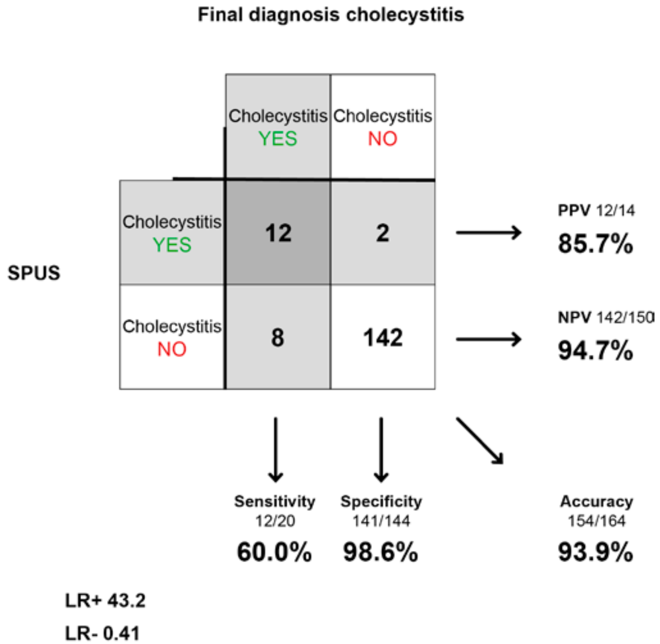


**Figure 11.** SPUS in diagnosing acute cholecystitis

The sensitivity for RPUS in diagnosing acute cholecystitis was 80.0%, specificity 97.8%, and accuracy 95.6%. $LR^+$ was 36.8 and $LR^-$ 0.41. The interobserver agreement (Cohen's kappa) between surgeons and radiologists for diagnosing acute cholecystitis was 0.61.

The results of SPUS in diagnosing acute appendicitis are shown in *Figure 12*. Sensitivity was 53.3%, and specificity 89.7%. The overall accuracy was 77.3%, $LR^+$ and $LR^-$ were 5 and 0.52 respectively.

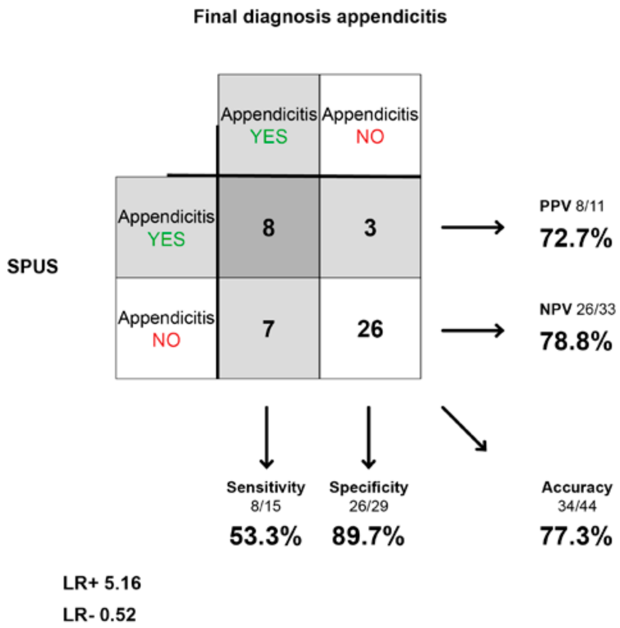


**Figure 12.** SPUS in diagnosing appendicitis

The sensitivity, specificity, and accuracy for RPUS in diagnosing appendicitis were: 73.3%, 93.3%, and 86.7%. $LR^+$ was 11.0 and $LR^-$ 0.29. Interobserver agreement (Cohen's kappa) between SPUS and RPUS for appendicitis was 0.41.

When interpreting these results, it is important to consider the prevalence of disease. Acute cholecystitis had a prevalence of 12% (20/164) in the cohort and the prevalence of appendicitis was 34% (15/44). The LR is less dependent on prevalence and makes it a more valuable measure compared with the predictive values, also presented in the figures.

## Paper III

This was a descriptive study, with the aim of evaluating morphological changes in the gallbladder during acute cholecystitis over time, using ultrasound. Of 120 patients enrolled in the study, 88 patients received at least one valid US examination. Thirty-seven of the patients were examined repeatedly and 51 had single examinations. Most of the patients (n=18) had two consecutive examinations (range 2-6 examinations). Cohort characteristics are shown in *Table 1.*

Mean gallbladder wall thickness was mostly stable, at around 4 mm during the observation time. Gallbladder volume was also stable with a slight tendency to decrease during the first days of observation. Gallbladder wall oedema was seen in 36 out of 37 patients with repeated examinations and in 46 out of 51 patients with single examinations, as shown in *Table 1*.

Patients who did not have gallbladder oedema at examination, commonly had a longer duration of symptoms (around seven days from onset of symptoms). However, oedema was present in five patients, with duration of symptoms of more than seven days.

Originally, it was planned to include surgeon-performed US in an effort to further validate SPUS in acute cholecystitis. A brief correlation calculation was performed during data analysis, however, and it was decided to exclude SPUS, due to the presence of a systematic bias in the examinations. Surgeons seemed to overestimate the gallbladder wall thickness compared with sonographers and radiologists, thereby skewing the results. The reason for this has not been fully elucidated, although one possible explanation could be the inclusion of pericholecystic fluid in the measurement of the gallbladder wall, which systematically would increase wall-thickness measurements by a few millimetres. To make analyses more stringent, we therefore chose to only include patients that received one or more examinations by a professional sonographer or radiologist in the paper.

**Table 1.** Cohort characteristics

| | Multiple examinations (N=37) | Single examination (N=51) | Comparison between groups |
|---|---|---|---|
| **Sex** | F 21 (56.8%)<br>M 16 (43.2%) | F 34 (66.7%)<br>M 17 (33.3%) | p = 0.38† |
| **Age (median, range)** | 64.0 (33-93) | 60.0 (19-88) | p = 0.13§ |
| **BMI (median, range)** | 29.5 (20-40) [1] | 27.0 (19-48) [7] | p = 0.84§ |
| **Days of symptoms on arrival (median, range)** | 2 (0-10) | 1 (0-8) | p = 0.12§ |
| **Temperature °C (median, range)** | 37.4 (36.4-38.2) | 37.3 (36.3-39.3) | p = 0.91§ |
| **CRP (median, range)** | 113 (1-353) | 27 (1-337) | *p =0.01*§ |
| **WBC (median, range)** | 13.7 (2.5-22.8) | 13.0 (5.1-20.3) | p = 0.22§ |
| **ALT (median, range)** | 0.54 (0.19-9.32) [1] | 0.51 (0.19-8.82) | p = 0.97§ |
| **ALP (median, range)** | 1.7 (0.6-5.5) [4] | 1.4 (0.7-5.5) [2] | p = 0.33§ |
| **Bil (median, range)** | 16 (5-62) [1] | 11 (4-89) [2] | p = 0.13§ |
| **Cholecystitis severity grade** | **I** 10/37 (27.0%)<br>**II** 27/37 (73.0%) | **I** 18/51 (35.3%)<br>**II** 33/51 (64.7%) | p = 0.49† |
| **Acute surgery** | Y 11/37 (29.7%)<br>N 26/37 (70.3%) | Y 32/51 (62.7%)<br>N 19/51 (37.3%) | *p < 0.01*† |
| **Gangrenous cholecystitis** | 4/11* | 5/32** | p = 0.20† |
| **Antibiotics** | | | |
| **- Prophylactic (single dose)** | 6/37 | 23/51 | *p = 0.01*† |
| **- Treatment** | 24/37 | 20/51 | |
| **- Not given** | 7/37 | 8/51 | |
| **Number of examinations** | 2 (n = 18)<br>3 (n = 12)<br>4 (n = 6)<br>6 (n = 1) | 1 (n = 51) | - |
| **Presence of oedema** | 36/37 | 46/51 | p = 0.39† |

Number of patients with missing data in brackets [ ]

† – Fisher's exact test

§ – Mann-Whitney U-test

Histopathology available for * 7/11 and ** 24/32 patients respectively.

## Paper IV

Of 135 054 patients recorded in GallRiks between 2006 and 2017, 11 153 were included in the analyses. A complication within 30 days was registered for 1573 of 11 153 patients (14.1%). The proportion of complications in the out-of-hours group was higher than in the office-hours group (15.6% versus 13.6%, crude OR 1.18 (95% CI 1.04-1.33)), but this difference disappeared when adjustments for confounders were made. The adjusted OR was 1.12 (95% CI 0.99-1.28). Factors most strongly associated with complications were age and ASA-score. The proportion of open procedures was higher in the out-of-hours group (37.9% versus 28.7%, adjusted OR 1.39 (1.25-1.54)), while operative time exceeding 120 minutes was less common when surgery was performed out of hours (40.4% versus 55.8%, adjusted OR 0.63 (0.58-0.69)).

There was a striking change in surgical technique during the study period. Between 2006 and 2009 around 50% of the procedures for acute cholecystitis were completed as an open procedure. Between 2009 and 2017 there was a gradual change towards a dominance of laparoscopic procedures, as can be seen in *Table 2*.

**Table 2.** Method of approach

| | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 |
|---|---|---|---|---|---|---|---|---|---|
| **Lap Surgery (%)** | 494 (53.4) | 560 (54.4) | 681 (60.3) | 680 (63.8) | 768 (69.0) | 892 (71.4) | 1063 (71.7) | 1188 (78.4) | 1359 (83.8) |
| **Open surgery (%)** | 431 (46.6) | 470 (45.6) | 449 (39.7) | 386 (36.2) | 345 (31.0) | 357 (28.6) | 419 (28.3) | 328 (21.6) | 263 (16.2) |
| **Total number (%)** | 925 (100) | 1030 (100) | 1130 (100) | 1066 (100) | 1113 (100) | 1249 (100) | 1482 (100) | 1516 (100) | 1622 (100) |

Extracted from the data, although not presented in Paper IV:

The frequency of conversion from laparoscopic to open surgery was stable at approximately 15% during the study period, both during office hours and out of hours. A significantly greater proportion of surgery was started as an open procedure in the out-of-hours group, 22.4% (608/2710) *versus* 12.6% (1067/8443) in the office-hours group.

With regards to complications within 30 days, there was a significantly higher proportion of complications within 30 days for patients that underwent open surgery, regardless of time of day of the procedure: 22.0% (760/3448) for open surgery, *versus* 10.5% (804/7685) for laparoscopic surgery, crude OR 2.42 (2.17-2.70).

Results indicate that, in addition to age, and ASA-score, open procedures contribute to the increased number of complications seen in conjunction with surgery out of hours.

# General discussion

The major novel findings of this thesis will be summarised and discussed in this section.

A high accuracy for surgeon-performed ultrasound in diagnosing gallstones was found. The use of surgeon-performed ultrasound in diagnosing acute cholecystitis and appendicitis is limited but may be considered an aid in confirming these diagnoses. However, the use of ultrasonography in preoperative risk scoring for acute cholecystitis needs to be further evaluated. Our results suggest that an updated same-day US, to look for presence of oedema might be valuable, as it may be possible to ascertain whether the patient would still benefit from acute surgery, irrespective of the amount of time having passed from the onset of symptoms or from admission to hospital. Performing cholecystectomy out-of-hours in patients with acute cholecystitis is not necessarily associated with complications, but should possibly be avoided for other reasons, not least due to the increased risk of open surgery with its attendant increase in morbidity.

The aim of the first two studies was to validate surgeon-performed US in the common surgical diagnoses of gallstones, acute cholecystitis, and appendicitis. A lower sensitivity for detecting gallstones was found, compared to previous studies where sensitivities in the range 95–100% have been described [90, 97, 98, 117]. These studies had a higher prevalence of gallstones in the study population, and the included patients were clinically suspected of having biliary disease, which may have led to an overestimation of the sensitivity. Larger studies, performed in an acute setting, demonstrate results similar to ours, including level of sensitivity. In a prospective study from 1999, of 496 patients with acute abdominal pain, the sensitivity for biliary tract disease (not further specified) was shown to be 91% for SPUS[95]. In a more recent (2008) retrospective study of 575 gallbladder examinations performed by emergency medicine doctors, sensitivity was 88% and specificity 87% in detecting gallstones[118]. It seems more complicated to diagnose acute cholecystitis and appendicitis using ultrasound, compared with the detection of gallstones. Although a small number of studies have shown exceptionally accurate results for SPUS, bedside US in the ED, as well as RPUS for these diagnoses[119, 120], the results from Paper II are well consistent with the reviewed literature and larger studies[83, 106]. In a systematic review by Carroll *et al.*, included studies showed results with higher sensitivity and specificity than in our study[100]. However, in several of the included studies the inclusion criteria were quite narrow and the prevalence of disease (appendicitis or gallstones) was considerably higher, which might have influenced the results[121].

In the first two studies (Papers I and II) we chose to include all patients referred to the radiology department for an abdominal scan. Not all of these patients presented with right upper or right lower quadrant pain, nor were referred with the specific question of biliary tract disease or appendicitis. This may have led to a wider range of differential diagnoses having to be excluded at the time of the examination, which could have influenced the performing clinician. Moreover, the broader range of clinical presentations in the included patients may be more reflective of true clinical practice, where a large number of unselected cases are assessed in the ED.

Paper III is, as far as we know, the first study to systematically observe ultrasonographic changes in the gallbladder during the early phase of the disease. We found that the presence of oedema in the gallbladder wall was stable over time. There were only a few patients who did not exhibit gallbladder wall oedema and these patients had in common a longer history of symptoms (more than seven days), except for one patient who was probably examined during the earliest phase of inflammation. There is a possibility that the oedematous phase of inflammation ends around seven days from onset of symptoms, which supports the recommendation of surgery performed within this time frame[29]. On the other hand, a few patients in this cohort had oedema present more than one week after onset of symptoms. These patients could theoretically have benefited from surgery, despite the recommended time frame in existing recommendations having been exceeded. Some of these patients did undergo surgery, but the outcome of these procedures lies beyond the scope of this thesis. Nonetheless, the data may well be of interest for future research. Gallbladder wall thickness decreased over time in the majority of patients. There was a tendency towards a reduction of median gallbladder volume during the first days from admission. These findings are difficult to compare since there is a lack of studies detailing ultrasonographic morphological changes of the gallbladder. The nature of this study was mainly descriptive, without hypothesis testing. The study could be regarded as hypothesis-generating, with the possibility to construct a sophisticated risk-scoring model, based on timing of the ultrasound examination in relation to the onset of symptoms, and presence of oedema together with other, already known predictive factors for difficult surgery in acute cholecystitis[110, 122, 123].

To further investigate factors contributing to complications after surgery for acute cholecystitis, we studied time of day for surgery as a possible risk factor. The large register-based cohort study performed in Paper IV, revealed a higher risk for complications for surgery out-of-hours, compared to office-hours. However, the risk did not persist after adjusting for confounders. Age and ASA were the factors most strongly associated with complications (irrespective of when surgery was performed), and the highest risk for complications was seen among the oldest patients with ASA-scores of 3 to 5. Furthermore, sex, BMI, and hospital-specific features all seemed to be more highly associated with outcome than time of day for surgery. Out-of-hours surgery was associated with an increased number of open procedures but a lower proportion of procedures exceeding 120 minutes.

These results are in line with previously reported studies[8, 9, 76], but the cohort in our study was larger. We found a significantly higher risk of open surgery, when the procedure was performed out of hours. The proportion of open procedures (including conversions from laparoscopic surgery) was high (30.9%). This proportion is considerably larger than in comparable studies[8, 9, 76]. These findings may be explained by the length of the study period (2006-2017). It should be taken into account that until the mid 90's, open cholecystectomy was the standard procedure for acute cholecystitis, and cholecystitis was considered a relative contraindication for laparoscopic surgery[124]. The decision to perform an open cholecystectomy, or to convert a laparoscopic procedure to open, is mainly due to difficult surgical conditions. Known preoperative risk factors for conversion apart from acute cholecystitis include male gender, age over 60 years, gallbladder wall thickness greater than 4-5 mm, and a contracted gallbladder[125].

# Methodological considerations

## Internal validity

To assess the internal validity of the included studies (how well they were designed and performed), one must address possible systematic and random errors within each study that could influence the results.

### Limitations in study design

All papers included in this thesis were observational cohort studies. Papers I and II, were based on the same cohort, the size of which was the result of a power calculation performed to assess SPUS in diagnosing gallstones. The power calculation behind Paper I yielded 190 patients, in order to detect a systematic difference between how often surgeons *versus* radiologists found gallstones. The number of patients reached, however, was only 179, increasing the risk of a type II error. Despite the smaller-than-anticipated population however, a difference was found, supporting the validity of the results. In Paper III the original intention was to also evaluate SPUS for patients with acute cholecystitis, but to ensure the quality of examinations, a highly experienced sonographer, with many years of training, or a radiologist specialising in US were assigned to perform the examinations. In Papers I-III data were collected prospectively and in the register-based cohort of Paper IV, data were collected retrospectively. In terms of causality there are some familiar concerns generally associated with observational studies, discussed below.

### Selection bias

In Papers I and II, patient enrolment required surgeon availability at presentation and study patients were not consecutive. This leads to a risk of selection bias, *i.e.* the studied population not being representative of the target population. It is possible that other factors could have contributed to a RUQ scan not being performed by the surgeon, such as anxiety of the patient or perceived examining difficulties by the surgeon also contributing to a certain selection. We consider this risk to be limited, as a parallel protocol for excluded patients was kept, where the reason of exclusion was stated.

The same reasoning can be applied to Paper III, where the availability of a sonographer on the ward was crucial for patient inclusion. The staff nurse, or staff surgeon on the ward were assigned to alert the sonographer for each patient that arrived with suspected or verified acute cholecystitis. The extent to which this was done varied throughout the study period, probably due to varying awareness of the on-going study among staff, and possibly due to varying workload on the ward. We tried to limit this error by examining the ward register to identify possible candidates for inclusion. The availability of the examiner was reasonably high, and 120 patients were examined in total over a period of 13 months.

In Paper IV, a large number of patients who underwent surgery for acute cholecystitis could not be included, due to lack of registration of time of day in GallRiks. Of approximately 26 000 patients, 11 153 were included in the study. The registration of time differed a lot between centres and it is possible that this might have contributed to a systematic selection of patients and centres. In the logistic regression analyses performed, attempts were made to adjust for hospital-specific factors regarding how time was registered, as well as how often surgery out of hours was performed at each centre.

## Information bias

The blinding in study I and II may not have been perfect. There was a possibility of patients overhearing findings and revealing the result of the previous examination, thus influencing the latter examiner's investigation (observer bias). We tried to limit this error type by documenting objective findings to the extent possible.

## Misclassification

A certain amount of misclassification bias could be expected in all studies, where patients might have been inadequately classified. In the register from which the study population in Paper IV derived, some patients might have been falsely diagnosed with acute cholecystitis in the register, and some patients with the disease might have been erroneously classified as not having the disease. This would most likely be an example of non-differential misclassification (misclassified patients being equally distributed between study groups). The size of the studied population and the high validity of the register[115] are two factors that contribute to minimise the effect of misclassification. Another example of misclassification could have been the definition of "out-of-hours", which might differ between centres. We chose to split the 24 hours into two 12-hour parts (between 19.00 and 7.00) in order to capture the procedures differing the most from daytime surgery. This was done to minimise the influence from procedures being performed right after office hours (which in Sweden generally would end at 17.00), due to stretching the working hours and/or to finish procedures initially planned as office-hours surgery.

## Confounding bias

The logistic regression analyses in Paper IV were made to adjust for possible confounders, *i.e.* factors being independently associated with both exposure and outcome. There is always a risk of unknown confounders not adjusted for in the model that might bias the results. We considered BMI to be a possible confounder based on previous studies[126], indicating more complicated surgery in these patients, especially during open procedures, but since BMI was missing to a large extent in the register, analyses were made without BMI. For complications within 30 days, we did perform a logistic regression analysis with BMI included, and the result did not differ from that presented. Also, more recent evidence indicates that there is no association between BMI and complications from laparoscopic cholecystectomy[127, 128].

### Collider bias and mediation

The results from Paper IV showed a large proportion of open surgery being performed out of hours. Open surgery was also associated with complications. One could argue for inclusion of open surgery as a confounder in the model for complications. We believe that this would however result in collider bias, since open surgery can be causally associated with the exposure variables age/ASA-score, time of day for the surgery, as well as with complication (outcome). It also represents a mediator on the pathway between time of day and complication. Adjusting for open surgery would result in over-adjustment and influence the causal relationship between time of day and complication.

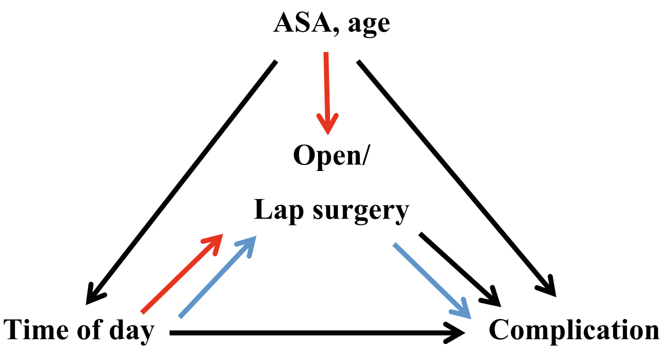


**Figure 13.** Directed acyclic graph over causal associations. The red arrows indicate that open/lap surgery represents a collider on the pathway between exposure variables and outcome. It also represents a mediator on the pathway between time of day and complications (blue arrows).

### Residual confounding

Factors that are inadequately measured could have a residual confounding effect and this applies to all the included studies to some extent. Unknown factors, or factors not possible to adjust for in Paper IV, could possibly confound the studied associations as previously mentioned. To split continuous variables into categories exemplifies another risk of residual confounding in this paper. The residual confounding effect on the estimates and can both increase and decrease the true association.

### Random errors

There is always a risk of random errors occurring when transferring data in the construction of a database, *e.g.* from study protocols. In Papers I and II, the database was cross-checked against study protocols, by two different individuals engaged in the project, which hopefully helped minimise the risk of random errors.

## External validity

### Generalisability

Using multiple radiologists, and thus multiple individuals with various experience as a reference standard might have had an influence on our results, as compared with using one US specialist as an expert examiner. However, using several radiologists might reflect a more realistic clinical situation where the US examination would be performed by the available radiologist on duty. The results from Paper IV, a population-based cohort study based on data from a national register with high coverage, are probably representative of the Swedish population and may be applied to any population in a similar Western country.

### Finding the whole truth and nothing but the truth

The absolute truths of the world are difficult to encounter and define, especially when moving from the narrower view of a specific investigation, to a wider perspective. This thesis represents no exception. In other words, some simplifications and suppositions had to be made in order to be able to address the research questions presented. An example of this is the use of an observer-dependent analysis tool as the gold standard reference, *i.e.* RPUS in Paper I. Even if RPUS has been repeatedly validated in the literature for diagnosing gallstones, the analysis method comes with an amount of uncertainty. In Paper II the uncertainty is exemplified by the final diagnosis used as reference, set by an external observer, but nevertheless a human interpreting medical records. There is also the concern of defining acute cholecystitis, the base for Papers III and IV, a criteria-based diagnosis, rendered from different modalities and the result of different clinical judgments. Furthermore, acute cholecystitis is classified into different grades, based yet on another interpretation of the severity of disease. No method of analysis is perfect, which is applicable for any interpretation of causal association. We can use the tools of statistics but we always have to compromise at some point during an investigation. We have tried to use established standards, which enables reproducibility and simplifies comparison with other work.

In this thesis, effort has been put into conducting the studies in such a manner that will minimise the risk of systematic errors. A central issue has been to use an investigator-dependent imaging technique to find the characteristics of a dynamic disease process, which might change by the day. It has become clear that even gold standards hold a level of uncertainty and imperfection. Chasing the truth of valid US examinations will not be facilitated if the reference method is lacking validity in itself. We might never find the absolute truths, but through assiduous scientific research, we can come closer to truth by continuously dispatching what is not proven to be true.

*Errare humanum est, ignoscere divinum*

The previous reasoning might be an example of unnecessarily complicating the conditions for research, and interpretation of results. On the other hand, it might represent a reflection of the beauty of the imperfections of the world.

# Conclusions

With training, surgeons can accurately diagnose gallstones, using ultrasound. Surgeon-performed ultrasound can be used as a piece to the puzzle of diagnosing acute cholecystitis and appendicitis but should not be solely relied on to exclude these diagnoses.

Same-day ultrasound could possibly aid in risk scoring patients with acute cholecystitis, evaluated for surgery. The presence of oedema in the gallbladder wall might play a role in deciding whether the patient is suitable for surgery or not but needs further evaluation.

Out-of-hours surgery is not associated with an increased risk of complications in patients with acute cholecystitis, but with a higher proportion of open surgery. The morbidity in patients undergoing open surgery should be taken into account when making decisions regarding surgery for acute cholecystitis.

# Clinical implications and future perspectives

The main clinical implication from the earlier studies is that SPUS is reliable when examinations result in a positive finding. When there is a clinical suspicion of gallstones, and the SPUS shows a negative finding, the examination should be completed with radiologist-performed US. A similar approach could be used for US in acute cholecystitis and to some extent also for appendicitis. A negative examination does not rule out the diagnosis, but a positive examination increases the probability of the diagnosis, which is indicated by the positive likelihood ratios found. One must keep in mind though, that in Paper II the number of cases were quite low, and the hypothesis testing was not based on a power-calculation for these diagnoses.

The use of POCUS by surgeons can be particularly useful for critically ill patients, when there is a need for a rapid bedside evaluation, to detect diagnoses that imply immediate and possibly life-saving interventions. The role should not be to replace radiologist-performed US, but to complement the surgeon's physical examination. It is probably preferable that the use is limited to examinations with binary diagnostic questions, rather than to investigate highly specific diagnostics. The value of POCUS is high in an emergency situation, especially out-of-hours, when rapid access to a radiologist or a sonographer might be limited.

The growing use of POCUS has increased the need of standardised US training. It has been discussed whether it should be a part of the surgical training for residents or even a part of the undergraduate medical education[96, 129]. Current recommendations for US training for surgeons are based on expert society recommendations rather than high-level evidence[92, 96, 102]. As POCUS inevitably is here to stay, there is a need for further validation of these US examinations.

US training as well as investment in equipment is associated with costs, and it is important to define the amount of initial and continuous training needed in order to reach and maintain an adequate level of US competence. Further studies aiming to validate how to maintain US skills would add valuable information to this question. The presence of a learning curve for novices performing US of the RUQ has previously been studied in emergency physicians[101], where the authors found that full agreement with the expert examiner was generally reached after performing 25 scans, suggesting that this amount might suffice as practice in a US training program to perform accurate RUQ scans.

When exploring this field of research, it would be interesting to further investigate whether a same-day preoperative US examination could help predicting difficult surgery for patients with acute cholecystitis. This research question has been raised and repeatedly discussed during this doctoral project. Within the framework of study III, we collected data from all cases that underwent surgery. A further study is planned to investigate whether the ultrasound-parameters identified in Paper III can be used as predictors for difficult surgery in acute cholecystitis. To be able to make any sort of inference from this, however, a bigger study population is needed.

There is a possibility that surgery for acute cholecystitis could be performed around the clock to a greater extent in the future. Our study showed no obvious contra-indication to out-of-hours surgery. However, the higher risk for an open procedure is an important aspect to consider, due to the increased morbidity for the patient. It is possible that the proportion of open procedures as a whole will continue to decrease in the future, also for the difficult cases, as laparoscopic proficiency increases, while at the same time, open proficiency and training decreases. To implement the performance of surgery 24 hours, seven days a week for acute cholecystitis and similar diagnoses, a complete reorganisation of the health care system would likely be necessary.

## Clinical implications based on study results

| | Yes | To some extent | No | Needs further investigation |
|---|---|---|---|---|
| SPUS for Gallstones | X | | | |
| SPUS for Acute cholecystitis | X | | | |
| SPUS for Appendicitis | | X | | |
| SPUS in risk scoring acute cholecystitis | | | X | X |
| Cholecystectomy out of hours | | X | | |

# Sammanfattning på svenska

En av de vanligaste anledningarna till att patienter söker på akutmottagningen med buksmärta är symptomgivande gallsten. Den vanligaste komplikationen till gallsten är inflammation i gallblåsan, akut kolecystit. För att identifiera gallsten och för att diagnostisera akut kolecystit är användningen av ultraljud central. Idag kan behandlande läkare utföra en basal ultraljudsundersökning direkt vid patienten, så kallat ”bedside ultraljud”. En sådan undersökning, utförd av kirurg, kan utgöra en tidsbesparande diagnostisk resurs för kirurger som bedömer patienter med misstänkt gallsten och kolecystit. Emellertid saknas stora valideringsstudier avseende noggrannhet och tillförlitlighet för dessa undersökningar.

Studie I och II utfördes för att validera kirurgiskt ultraljud för vanliga kirurgiska diagnoser (gallsten, kolecystit och blindtarmsinflammation). Vi fann att kirurgiskt ultraljud är tillförlitligt för att hitta gallsten, med en noggrannhet på 94,4%, och nådde en hög nivå av överensstämmelse med radiologiskt ultraljud. Det är mer utmanande att diagnostisera akut kolecystit och blindtarmsinflammation med ultraljud. De sammanlagda resultaten antyder dock att kirurgiskt ultraljud kan användas som hjälp för att bekräfta, men ej för att utesluta dessa diagnoser.

Vid upprepade gallstensanfall eller vid akut kolecystit kan patienten bli aktuell för operation. För patienter med akut kolecystit är tidpunkten för operationen, i förhållande till grad av inflammation, viktig. En av de viktigaste kliniska frågorna är hur man kan misstänka, och/eller förutspå när en operation för akut kolecystit kommer att bli svår, vilket ökar risken för komplikationer. Idag förlitar vi oss mycket på tid från symptomens början när vi fattar beslut om operation. Vi vet att patienter med kolecystit bör opereras vid den första akuta inläggningen på sjukhus. Den granskade litteraturen stöder kirurgi inom 72 timmar efter ankomst till sjukhus, eller inom 5-7 dagar från symptomens början. Det finns dock inga rekommendationer vad man ska göra omedelbart efter att de 72 timmarna har passerat. Vissa patienter har sannolikt fortfarande nytta av en operation vid samma vårdtillfälle, medan andra har större nytta av en senarelagd, planerad operation. Detta beror på potentiellt ökade tekniska svårigheter vid själva operationen, med begynnande ärrbildning och fibros som kan förväntas efter en viss tid, tillsammans med en kvarvarande ökad blodförsörjning i området, som förekommer vid en akut inflammation. En senarelagd operation är tänkt att äga rum när inflammationen har läkt ut.

Man vill i möjligaste mån undvika långa väntetider till operation för inneliggande patienter med akut kolecystit. Frågan om att utföra kirurgi dygnet runt (jourtid) på dessa patienter har kommit att diskuteras i detta sammanhang. Det finns begränsad evidens för hur det går för patienter som genomgår akut kolecystektomi på jourtid. Följderna av eventuella skador på centrala kärl eller gallgångar, på grund av en trött eller oerfaren kirurg kan vara förödande, innebära komplex rekonstruktiv kirurgi, och eventuellt allvarliga men för resten av patientens liv. I studie IV har vi undersökt om operation av akut kolecystit på jourtid är associerat med en högre grad av komplikationer. Det visar sig att den högre graden av komplikationer som ses på jourtid snarare beror på en högre ålder och en ökad sjuklighet hos patienterna än vad den beror av tid på dygnet.

Patienter med akut kolecystit skiljer sig åt gällande hur symptom presenteras, i grad av inflammation och hur svår operationen blir vid operationstillfället. En patient kan vara väl lämpad för operation medan en annan kan ha hög risk för komplikationer, trots att samma tid har passerat sedan symptomen började. Det finns ett behov av starkare vetenskapligt stöd bakom beslutsfattandet kring kirurgi för dessa patienter. Det skulle vara värdefullt att kunna fastställa en mer objektiv gräns, för när man ska vänta eller fortgå med akut kirurgi. En gräns som är mindre beroende av tid. Det vore en vinst för kirurgen att kunna förutspå eller förhindra en svår operation. Ett tänkbart sätt är att använda ultraljud till detta. I studie III har vi försökt beskriva det naturliga förloppet av akut kolecystit med hjälp av upprepade ultraljudundersökningar. Undersökningarna utfördes dagligen varje dag som patienten vårdades inneliggande på sjukhus, i väntan på operation eller utskrivning. Vi mätte gallblåsans volym, väggtjocklek och tittade efter förekomst av ödem i gallblåseväggen. Vi fann att gallblåsans väggtjocklek såväl som volymen visade en tendens att minska över tid. Förekomsten av ödem i gallblåseväggen var stabil. Gemensamt för patienter utan ödem var en lång sjukhistoria med långvariga symptom. Studien var främst hypotesgenererande och man kan utifrån resultaten överväga huruvida ödem i gallblåseväggen och tidpunkt för själva ultraljudsundersökningen bör läggas till befintliga faktorer i riskbedömning av svår kirurgi för akut kolecystit.

Det övergripande syftet med detta forskningsprojekt var att validera kirurgiskt buk-ultraljud för vanliga kirurgiska tillstånd som gallsten, akut kolecystit och blindtarmsinflammation samt att optimera vården för patienter med akut kolecystit. Kan vi lära oss att bättre avgöra när akut kirurgi ska utföras, när en operation skall skjutas upp, eller till och med undvikas, för att minimera risken för komplikationer?

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