

Gallstone-related symptoms and quality-of-life

in patients undergoing gallstone surgery

The Gothenburg Gallstone Questionnaire (GGQ24)

Simon Henry Pålsson

**DEPARTMENT OF SURGERY
INSTITUTE OF CLINICAL SCIENCES
SAHLGRENSKA ACADEMY, GOTHENBURG, SWEDEN**



UNIVERSITY OF GOTHENBURG

GOTHENBURG 2022

Cover illustration: The tree of bile by © Siri Pålsson 2022

Gallstone-related symptoms and quality-of-life in patients undergoing
gallstone surgery - The Gothenburg Gallstone Questionnaire (GGQ24)

© Simon Pålsson 2022
simon.palsson@gmail.com

ISBN 978-91-8009-727-7 (PRINT)
ISBN 978-91-8009-728-4 (PDF)

Printed in Borås, Sweden 2022
Printed by Stema Specialtryck AB



*To my girls –
the loves of my life*

***“Life is not all about reaching the next goal –
It is mostly about appreciating what you have”***

Your caring husband and father

ABSTRACT

<p>Department of Surgery Institution of Clinical Sciences Sahlgrenska Academy University of Gothenburg Gothenburg, Sweden</p>	<p>DOCTORAL DISSERTATION Author: Pålsson S.H. MD</p>
<p>Date of issue May 20th 2022</p>	
<p>Title and subtitle: Gallstone-related symptoms and quality-of-life in patients undergoing gallstone surgery - The Gothenburg Gallstone Questionnaire (GGQ24)</p>	
<p>Background: Patients with symptomatic gallstone disease can present with years of intermittent suffering or acute complicated disease. The only definitive cure is surgery. Registering both surgical and patient reported outcome measures may provide a more reliable platform to assess the impact of gallstone surgery and improved decision-making.</p>	
<p>Methods: Retrospective patient cohorts from the national quality registry for Gallstone Surgery and ERCP, Gallriks, served as study groups in paper I-IV. These groups were crosslinked with the National Patient Register, Statistics Sweden, Central Death Register and the Swedish Prescribed Drug Register to obtain valid and reliable data. Paper V is a prospective qualitative mixed methods design using guidelines for item-development from the International Society of Pharmacoeconomics and Research (ISPOR) including focus group interviews, expert team reviews, cognitive debriefing, and other psychometric analyses.</p>	
<p>Results: The 36-Item Short Form health survey (SF36) proved to be a highly responsive tool for measuring HrQoL 6 months after surgery. Cholecystectomy gave a significant improvement in QoL (Paper I). Subgroups in the Swedish population with different socioeconomic variables did not show any difference in incidence or outcome of surgery. The presentation of the disease and the timing for surgery differed between the genders (Paper II). Patients over 80 years are associated with increased postoperative morbidity but may benefit substantially from surgical intervention. Laparoscopic approach was associated with significantly less mortality than open surgery or conversion, and lead to shorter hospital stay (Paper III). Perioperative myocardial infarction after gallstone surgery is more frequent among the elderly. A previous Non-ST Elevation Myocardial Infarction (NSTEMI) within 8 weeks prior to surgery was the most important predictor of a 30-day postoperative MI. The postoperative 30-day risk for MI was 52.8%. After 8 weeks it gradually reached the risk of the background population (Paper IV). 367 QoL statements were generated from focus groups. Following question reduction, statistical and psychometric evaluation, a disease-specific PROM formula was developed with 24 preoperative and 21 postoperative questions – The GGQ24 (Paper V).</p>	
<p>Conclusion: Gallriks and other Swedish national registers offer high quality data for research. Cholecystectomy does not differ in incidence or outcome in relation to socioeconomic subgroups in Sweden. Gallstone surgery can be performed safely in patients over 80 following careful preoperative selection. NSTEMI independently is the greatest risk factor of a 30-day postoperative MI following cholecystectomy. GGQ24 is a disease specific PROM-instrument that will contribute to decision-making and care of patients undergoing gallstone surgery.</p>	
<p>Key words: Cholecystectomy, Gallstone disease, Laparoscopic surgery, Quality-of-Life, PROM, Cholelithiasis, Vesica Fellea, Bile Stones, Biliary disease, Cholecystolithiasis, Myocardial Infarction</p>	
	<p>Number of pages: 61</p>
<p>ISBN PRINT: 978-91-8009-727-7</p>	<p>ISBN PDF: 978-91-8009-728-4</p>

POPULÄRVETENSKAPLIG SAMMANFATTNING

Kirurgi med borttagande av gallblåsan, så kallad kolecystektomi, är ett vanligt kirurgiskt ingrepp som utförs sekundärt till gallstenssjukdom. I Sverige utförs ca 15 000 kolecystektomier årligen. Behovet av kirurgi uppkommer från symptomgivande gallstenar eller komplikationer som uppstått av gallstenssjukdomen.

Förekomst av gallstenar är vanligare hos kvinnor och med stigande ålder. Riskfaktorer är bland annat kvinnligt kön, ålder, fetma, snabb viktnedgång och graviditet. Bildandet av gallstenar beror på att ämnen i gallan, vanligtvis kolesterol eller hemoglobin som brutits ned från blodet, kristalliserar sig. När gallstenar väl har bildats kan de orsaka smärtsamma kramper i magen och stoppa upp flödet av galla i gallträdet vilket kan ge akut inflammation, gulsot, bukspottkörtelinflammation och blodförgiftning. Obehandlade kan komplikationerna leda till döden. Gallstenskirurgi har blivit mycket säkrare under de senaste 20 åren genom införandet av titthålskirurgi. I Sverige har även ett kvalitetsregister, Gallriks, införts för att mäta utfallet av kirurgin.

Denna avhandling innehåller 5 delarbeten, varav 4 publicerade i internationella tidskrifter och har fokuserat på gallstenskirurgi hos olika subgrupper i samhället, riskfaktorer och livskvalitet före och efter kirurgi. Delarbete 1 undersökte livskvalitet hos en grupp individer via ett frågeformulär som besvarades före och 6 månader efter gallstenskirurgi. Efter 6 månader sågs ingen signifikant förändring i livskvalitet gentemot bakgrundsbefolkningen. Den parameter som påverkades mest av kirurgi var kroppslig smärta.

Delarbete 2 undersökte hur kön och socioekonomiska faktorer påverkar incidensen av gallstenskirurgi och också om dessa faktorer påverkar utfallet. Resultatet visar att gallstenssjukdomen uppvisar olika presentation mellan könen och att kvinnor opereras sex ggr oftare än män på grund av smärtor i yngre ålder med topp kring 35-50 år. Män opereras i högre grad för komplikationer till gallstenarna under senare delen av livet med topp mellan 55-70 år. Inga övriga signifikanta skillnader sågs i de socioekonomiska grupperna.

I delarbete 3 undersöktes riskerna med gallstenskirurgi på personer över 80 år. 1960 operationer granskades. Dödligheten var 4 gånger högre än den ej opererade bakgrundsbefolkningen av samma kön och ålder. Faktorer som

ökade risken för död efter kirurgi i denna grupp var öppen teknik istället för titthålsteknik vid operation, hög samsjuklighet och manligt kön. Kirurgi är relativt säkert i denna grupp förutsatt att en noggrann värdering görs av patientens hälsostatus innan beslut om operation fattas och att säkerheten kan ökas ytterligare genom användandet av titthålskirurgi. Riskökningen för hjärt-kärlpåverkan efter kirurgi även bland patienter över 80 år är relativt låg. Frågeställningen till delarbete 4 uppstod. Vilka faktorer utgör störst risk för en hjärt-kärl-komplikation efter gallstenskirurgi? Här kunde vi fastställa, att patienter som har haft en sub-akut hjärtinfarkt (NSTEMI) inom 8 veckor före operation löper 4 ggr högre risk att drabbas av en ny hjärtinfarkt inom 30 dagar efter kirurgi. Om längre tid förlöpt är risken jämförbar med bakgrundsbefolkningen. Detta är ett viktigt beslutsstöd vid planeringen av tidpunkten för kirurgi.

Vid all kvalitetsmätning är det viktigt att registrera både sjukvårdens observationer och patientens egna upplevelser. För att kunna göra detta initierades delarbete 5 med avsikt att finna svar på de frågor som har störst vikt för patienter med gallstenssjukdom som opereras. Här har två frågeformulär tagits fram och analyserats för att sedermera kunna kondenseras ned till ett standardiserat sjukdomsspecifikt formulär, där vi kan mäta det patientupplevda utfallet.

Sammanfattningsvis har avhandlingen visat att:

- Svenska kvalitetsregistret Gallriks stora täckningsgrad och kvalitativa data utgör en pålitlig källa för vetenskaplig forskning
- Gallstenskirurgi i Sverige har goda resultat med hög postoperativ livskvalitet
- Äldre patienter över 80 år som selekteras rätt har stor nytta av kolecystektomi
- Socioekonomiska skillnader såsom inkomst, utbildning, etnisk bakgrund och kön påverkar inte selektionen för vilka som opereras och inte heller utfallet efter kolecystektomi
- Icke ST-höjningsinfarkt (NSTEMI) inom 8 veckor före operation är den största riskfaktorn för 30-dagars postoperativ hjärtinfarkt efter kolecystektomi
- Den bidragit till att ge en bättre bild av livskvalitetsförändringar vid gallstenssjukdom, stärkt beslutsstöd inför kirurgi hos olika socioekonomiska grupper och lagt grunden för att sjukdomsspecifikt kunna mäta det patientupplevda utfallet av gallstenskirurgi.

“You can never be overdressed or overeducated”

- *Oscar Wilde*

ORIGINAL PAPERS

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

- I. *Registration of Health-Related Quality of Life in a Cohort of Patients Undergoing Cholecystectomy*** – Pålsson SH, Rasmussen I, Lundström P, Österberg J; ISRN Gastroenterology (2011) Volume 2011, Article ID 507389

- II. *Influence of gender and socioeconomic background on the decision to perform gallstone surgery: a population-based register study*** – Pålsson SH, Sandblom G; Scandinavian Journal of Gastroenterology (2015) 50:2, 211-216

- III. *Outcome after cholecystectomy in the elderly – a population-based register study*** – Pålsson SH, Saliba G, Sandblom G; Scandinavian journal of Gastroenterology (2016) 51:8, 974-978

- IV. *Risk factors for postoperative myocardial infarct following cholecystectomy: a population-based study*** – Pålsson SH, Engström C, Enochsson L, Österlund E, Sandblom G; HPB (2020) Volume 22, Issue 1, January 2020, Pages 34-40

- V. *The development of a person-centred self-report instrument to investigate quality-of-life aspects of Gallstone surgery - The Gothenburg Gallstone Questionnaire (GGQ24)*** – Pålsson SH, Engström C, Skoog J, Redéen S, Rogmark P, Enochsson L, Prebner L-L, Österberg J, Linder F, Syrén E-L, Sandblom G, Chaplin J-E; (to be submitted spring 2022)

TABLE OF CONTENTS

ABBREVIATIONS	III
THESIS AT A GLANCE	V
1 INTRODUCTION	1
1.1 AETIOLOGY	4
1.2 EPIDEMIOLOGY AND SYMPTOMATOLOGY	7
1.3 RISK FACTORS	10
1.4 PREVENTION	12
1.5 TREATMENT	15
1.6 OUTCOME	18
2 AIM	22
3 MATERIALS AND METHODS	23
3.1 REGISTERS	24
3.2 DESIGN	29
4 RESULTS	35
4.1 PAPER I	36
4.2 PAPER II	38
4.3 PAPER III	39
4.4 PAPER IV	40
4.5 PAPER V	41
5 DISCUSSION	43
5.1 ETHICS APPROVALS	49
6 CONCLUSION	50
7 FUTURE PERSPECTIVES	51
ACKNOWLEDGEMENTS	52
REFERENCES	54

ABBREVIATIONS

AGMSP	Age and Gender Matched Standard Population
AHA	American Heart Association
ASA	American Society of Anaesthesiologists Classification
BDI	Bile Duct Injury
BMI	Body Mass Index
CBD	Common Bile Duct
CDR	Central Death Register
CI	Confidence Interval
CT	Computed Tomography
ECG	Electrocardiogram
ERCP	Endoscopic Retrograde Cholangio- Pancreatography
ESWL	Extracorporeal Shock Wave Lithotripsy
GGQ24	Gothenburg Gallstone Questionnaire
GIQLI	Gastrointestinal Quality of Life Index
GRM	Graded Response Model
HrQoL	Health-related Quality of Life
ICC	Item Characteristics Curves
ICD	International Classification of Disease
IRT	Item Response Theory
ISPOR	International Society of Pharmacoeconomics and Outcomes Research's task force

KMO	Kaiser-Meyer-Olkin index
LC	Laparoscopic Cholecystectomy
MI	Myocardial Infarction (heart attack)
NPR	National Patient Register
NSTEMI	Non ST Elevation Myocardial Infarction
NYHA	New York Heart Association
OR	Odds Ratio
PAF	Principal Axis Factoring
PRO	Patient Reported Outcome
PROM	Patient Reported Outcome Measure
PROMIS	Patient-Reported Outcome Measures Information System
QoL	Quality of Life
SD	Standard Deviation
SES	Social and Economic Status
SF36	36-Item Short Form health survey
SIR	Standardised Incidence Ratio
SMR	Standardised Mortality Ratio
SPDR	Swedish Prescribed Drug Register
SS	Statistics Sweden
STEMI	ST Elevation Myocardial Infarction

THESIS AT A GLANCE

	Research Questions	Methods	Results	Conclusions
I	<p>How does gallstone surgery affect HrQoL?</p> <p>How does HrQoL vary in a patient cohort undergoing cholecystectomy compared to the background population?</p>	<p>A quantitative retrospective study. Patient data from Gallriks. Patients from selected surgical units completed the SF36 pre- and 30 days postoperatively.</p>	<p>Preoperatively all sub scores were significantly lower than the age- and gender matched Swedish population. 6 months postop there was no difference between expected and observed QoL. The highest responsiveness was seen for bodily pain.</p>	<p>SF36 is useful for measuring the impact of gallstone surgery on QoL. The postinterventional health status equalled or even exceeded the age and gender matched Swedish population for all subscales.</p>
II	<p>How do socioeconomic risk factors influence the decision to perform gallstone surgery in Sweden?</p>	<p>A quantitative retrospective study. Patient data from Gallriks. Background data was cross linked with data from Statistics Sweden.</p>	<p>Socioeconomic risk factors have no impact on the decision to perform cholecystectomy. There is a significant difference in incidence of surgery due to age and gender. Women are operated on at an earlier age with a peak at 35-50 for women and 60-75 years of age for men. The presentation of the disease differs between the genders.</p>	<p>Management of the disease does not seem to deviate due to socioeconomic background. Women have a higher incidence which may explain surgery at wider indications. Men may be operated upon on stricter indications with higher risk of complications due to postponement of surgery.</p>
III	<p>Is it safe to perform gallstone surgery on the people over 80 years of age? How does comorbidity affect the risk of performing cholecystectomy in this age group?</p>	<p>A quantitative retrospective registry study. A patient cohort from Gallriks was cross linked with the Swedish Patient Register and The Central Death Register.</p>	<p>High Comorbidity score and Open surgery increased the postoperative mortality risk. No risk factor was independently increasing the risk for a cardiovascular event.</p>	<p>Gallstone surgery may be performed safely in most cases on people over 80 years or older. Cholecystectomy may be lifesaving for patients with gallstone complications.</p>

IV	<p>To identify the risk factors and analyse the incidence of myocardial infarct after cholecystectomy.</p> <p>Is there a cut-off in delay before gallbladder surgery that may be considered safe after recent MI?</p>	<p>A quantitative retrospective registry study. Data from Gallriks were matched with ICD-codes for STEMI and NSTEMI from the National Patient Register and data from the Swedish Prescribed Drug Register.</p>	<p>The risk for a 30-day postoperative MI was higher for patients with a previous NSTEMI. Men, age >50, patients with ASA 3 or higher and open approach or laparoscopic converted to open were independent risk factors. A previous MI within 8 weeks of surgery increased the risk of a postoperative MI to 52,8%.</p>	<p>Compared to the age and gender matched background population the risk of a postoperative MI increases three-fold after cholecystectomy. Of those who develop a postop MI, the mortality increases from 0.2% to 11.5%. Elective surgery should be delayed at least 8 weeks after a cardiac infarction.</p>
V	<p>How do we improve gallstone surgery by involving the patient reported outcome?</p>	<p>A qualitative prospective study. A mixed methods design was used including focus group interviews, existing disease specific questionnaires, cognitive debriefing, and an expert panel to develop an item bank. After item gap analysis a pre- and a postoperative pilot questionnaire was developed and distributed. Statistical and psychometric analyses were performed and a final disease-specific PROM with a pre- and a postoperative part was developed, the GGQ24.</p>	<p>600 pre- and 600 postoperative pilot questionnaires were distributed via post to the patient's home address. 104 preop and 167 postop were returned complete. Descriptive item statistics, internal reliability, IRT using the graded response model was performed and a final disease specific PROM was developed with a preoperative model of 24 questions in 8 domains and a postoperative model with 21 questions in 5 domains – the GGQ24.</p>	<p>The GGQ24 is a new disease-specific questionnaire developed according to current guidelines for PROM-questionnaires. The GGQ24 will be an important tool for comparing quality between operating units in Sweden including the patient reported outcome of surgery.</p>

1 INTRODUCTION

In 1420, a woman died with abdominal pain in Florence, post mortem diagnosed with gallstones by a pathologist named Antonio Benevieni, an event described as the first account of gallstone disease.¹ Around 200 years later, in 1687, Dr von Der Wiel encountered gallstones *en passant* in a patient with purulent peritonitis.² Biliary colic became a recognized condition, unfortunately without any standardized treatment. In 1743, the first reported drainage of the gallbladder was performed by Jean Louis Petit – the founder of gall bladder surgery², with drainage and removal of the gallstones. The procedure underwent improvement by Dr Marion Sims, who performed the first cholecystostomy for obstructive jaundice on a 43-year-old woman. Cholecystostomy was for many years the golden standard intervention for patients with biliary colic.^{3, 4}

In 1882 Dr Carl Langenbuch, chief surgeon at the Lazarus Hospital in Berlin, Germany, performed the first cholecystectomy at the age of 27, on a 43-year-old man who later was cured and discharged.⁵ The procedure was received with scepticism among other scientists and doctors.⁶ Nevertheless, in the early 20th century a study of mortality between patients undergoing cholecystectomy vs cholecystostomy was published, where the mortality rate after cholecystectomy was 12% compared to cholecystostomy 27%. The postoperative situation after cholecystectomy was associated with significantly less pain, no drainage, and a permanent cure.³

The cholecystectomy procedure gradually became widely accepted and 103 years later, the first laparoscopic cholecystectomy was performed by Prof Dr Eric Mühe of Böblingen, Germany in 1985.⁷ A French gynaecologist, Dr Mouret, is often credited for the first laparoscopic cholecystectomy. However, the procedure carried out by Dr Mouret took place two years later in 1987. He was performing a routine procedure when he noticed inflammation of vesica fellea (lat. Gallbladder) and removed it. The patient did not have any sequelae and was cured.⁸

Laparoscopic cholecystectomy was widely adopted and in the 1990:s considered golden standard treatment for symptomatic gall stone disease.⁹ For many years it was considered inappropriate on elderly due to fear of cardiopulmonary complications secondary to the increase abdominal pressure with iatrogenic carbon dioxide, but several studies have shown that it is a relatively secure intervention and often a life-saving procedure for this group.

¹⁰⁻¹³ The first laparoscopic cholecystectomy in Sweden was performed in 1991 by Dag Arvidsson.¹⁴

In Sweden, gallstone surgery is a very common procedure, and around 12,000 patients undergo cholecystectomy annually.

To assemble data about gallstone surgery, a nonmandatory quality register was established in Sweden during the 1990:s. The registry does not exist today but was an important first step towards today's validated National Quality Registry - GallRiks. Gallriks, established in 2005, has national cover in Sweden and has continuously provided high quality data.¹⁵ The primary purpose of GallRiks is to provide data on outcome after interventions aimed at gallstones, including open cholecystectomy, laparoscopic cholecystectomy and ERCP. Reports on the outcome at each unit can be retrieved by the local users. These reports are intended as benchmarks for quality and safety of care at the local units.

GallRiks is also a source for research on the management of gallstone disease.



The National Patient Registry (NPR), is a mandatory registry for all admitted patients in Sweden, provides data about inpatient and outpatient care, including management of gallstone disease. Statistics Sweden is a national register that includes data on education level, nationality and income.

Figure 1. Dr. Carl Johann Langenbuch

Patient experienced outcome and the impact on quality of life (QoL) are crucial outcomes in gallstone surgery. As the main purpose of routine gallstone surgery is to alleviate symptoms caused by the gallstones, the benefit from the procedure can only be fully understood if the patient perceived outcome is assessed in a standardised way. A general QoL registry was introduced in 1992 to better help us evaluate the patient perspective.¹⁶ During the 21st century, disease specific questionnaires have been developed to measure the patient-reported outcome (PRO).

PRO is considered an important instrument for assessing quality of care and is often included in quality registries. Specific guidelines have been established for the development of validated formulas.¹⁷

With the quality Registries as base and validated patient reported outcome measures as complement all aspects of the procedure relevant for the patient are covered. This would take us one step closer to provide the best possible care and the safest procedures – and to carefully select the patients that would benefit the most from the interventions at the lowest cost.

1.1 AETIOLOGY

Formed in the biliary system, gallstones are a benign condition secondary to an imbalance in the components of bile. Bile is generated in the liver and has two main functions; to excrete exogen and endogen toxins from the blood stream and to absorb nutrients from the intestine. Gallstones, also referred to as calculous biliary disease, are crystallized fragments of excessive amounts of cholesterol (cholesterol stones) or bilirubin /bilirubin combined with cholesterol (pigmented stones) assembled as “gravel” or “stones” within the biliary system. The condition itself is not dangerous and mostly asymptomatic but can lead to lethal complications secondary to obstruction of the biliary system such as jaundice, cholecystitis or pancreatitis. Cholesterol stones (yellow) usually consist of a combination of calcium and cholesterol – less than 10% are pure cholesterol stones. Pigmented stones are divided into black stones (from haem), primary generated in the gallbladder and associated with haematologic diseases such as sickle cell anaemia, haemolysis, thalassemia, hereditary spherocytosis or other conditions such as cirrhosis or splenomegaly; and brown stones, generally formed in the bile ducts and secondary to infection. Brown stones are precipitated by haemoglobin incorporated with cholesterol – hence the name and difference in colour. Both types have also been considered to vary with dietary changes. Cholesterol stones arise when the bile is over-saturated with cholesterol and there is an imbalance between pro- and anti-crystallizing factors.¹⁸ [Figure 3]



Figure 3. The Tree of Bile
Cover Illustration © Siri Pålsson with permission

Symptoms from gallstones are always secondary to an obstruction of a structure in the biliary tree, hence biliary colic is secondary to intermittent obstruction of the cystic duct from stones in the gallbladder and generally occur after a meal secondary to secretion of cholecystokinin (CCK), a peptide hormone excreted in the bloodstream when food enters the duodenum, causing the gallbladder to contract.

Several risk factors are known such as female gender, older age, prolonged fertility period from menarche to menopause, obesity, rapid weight loss, opioids, oestrogen therapy, and family history of gallstone disease. Asymptomatic gallstones are stones that do not obstruct any of the hollow structures in the biliary tree including stones that are passing through the system without causing obstructing. The prevalence of asymptomatic gallstones is increasing with age and has an estimated prevalence to be one fourth of all men and one third of all women at 80 years age.

- Gallstone formations are caused by a limited number of major factors
- Gallbladder dysmotility
- High intravesicular concentration of bile
- Crystal nucleation
- Super-saturation of secreted bile

Rapid processing of haemoglobin leads to increased risk for pigmented stones whereas secretion of high concentration of lipids and cholesterol in the biliary system are associated with cholesterol stone precipitation. In the gallbladder, the balance between calcium, bile acids (solutes for cholesterol) and cholesterol is affected by the absorption of sodium and water. When the solubility of cholesterol is exceeded, crystallization of cholesterol initiates. Other proteins as immunoglobulins and glycoproteins further accelerates the formation of stones.

In a super-saturated state, immobilisation of the gallbladder secondary to pregnancy, long-term fasting, use of total parenteral nutrition, post vagotomy or use of somatostatin analogues also increases the risk of lithogenesis.

When we address “gallstone disease” further on in this thesis, we are referring to cholesterol gallstone disease.

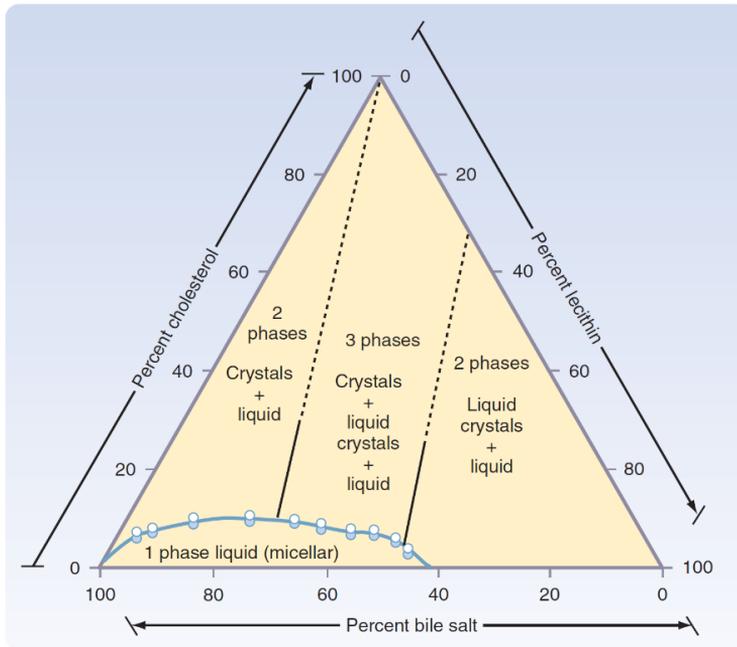


Figure 3. Triangle of Solubility. *J Clin Invest* with permission.

The saturation of bile is constituted by the molar ratio of phospholipids, cholesterol, and bile acids. Cholesterol is soluble in the lower left corner of the triangle, the area under the closed circles (blue dotted line) where a micellar solution exists. Between the empty and closed circles, cholesterol is super-saturated and only crystallized in a state with stasis. In the rest of the triangle, crystals form immediately.

1.2 EPIDEMIOLOGY & SYMPTOMATOLOGY

The prevalence of gallstones differs largely between different populations in the world, from very low in African and Asian populations to around 60-70% in American native populations. The median prevalence in Europe ranges from 5.9% in subpopulations in Italy to 21.9% in certain areas of the Nordic countries¹⁹ and is estimated to be an average of 10 - 20%.²⁰⁻²³ In Sweden the prevalence increases with age and at 75 years of age over 50% of the women and 30% of the men have the condition or have undergone biliary surgery.²⁴ About 10% - 20% of the affected individuals get symptomatic disease within 5 to 20 years respectively and only 0.3 - 1% of these turn into complications of the disease without a symptom onset. The risk for gallbladder cancer is also low at 0.02%, therefore prophylactic removal of the gallbladder is not warranted if the patient remains asymptomatic since it associated with a higher cost, a higher risk of complications without any benefit in survival.^{25, 26}



Figure 4. Cholesterol Cholelithiasis and Vesica Fellea (cut) from a patient with Cholecystitis chronica

Photo: Dr Darius Ribokas with permission

Symptomatic gallstone disease, referred to as biliary colic, is the most common presentation and accounts as indication for the majority of the cholecystectomies performed. It follows a distinct pattern in most cases and is described as painful cramps in the epigastrium or the right hypochondrium, often radiating towards the back and with referred pain around the right scapula and with duration for over 15 - 30 minutes appearing 1 - 24 hours after dietary intake. Intolerance of fatty foods and previous similar attacks are independent predictors of gallstones.²⁷⁻³⁰ Biliary colic attacks often result in high scores (VAS 9 - 10) on a 10-point pain scale, and interferes with rest and cause nausea

or vomiting. Biliary colic is not exclusively correlated with a postprandial state, in general not associated with pyrosis and is not relieved by bowel movements. If these symptoms are combined with fever, leucocytosis or icterus - with or without peritonitis - complicated disease must be suspected.^{27-29, 31}

Correctly identifying the pain attack is of great importance since it is generally accepted as the indication for treatment. Experiencing characteristic pain attacks for gallstone disease may depend on differential diagnoses (see below) have a low prediction for gallstone disease whereas their absence has a high correlation with not having gallstones.^{27, 28}

Pain arising from gallstones is generated from gallstones obstructing the outgoing bile flow in the cystic duct or the Ampulla Vateri, causing distension in the biliary tree or the gallbladder and activating of visceral sensory neurons.³²

Defining abdominal pain due to gallstones is challenging.²⁸ Differential diagnoses include a wide range of abdominal conditions, (abscessus abdominis, ulcus duodenale perforans, diverticulitis, hepatitis acuta, pancreatitis), cardiac (perimyocarditis), neurological (radiculopathia thoracica) and vascular disorders (thrombosis vena mesenterica superior). To avoid situations with remaining pain after cholecystectomy, preoperative evaluation to rule out differential diagnoses is crucial. Berhane et al. showed in a prospective study of 220 patients with known symptomatic gallstone disease that a majority of patients can identify a punctum maximum of pain, that the pain attacks were mainly in the evening or the night with a duration of more than 30 minutes and that the majority of patients experience functional disorders such as reflux or pyrosis. A systematic review from 2009 by Berger



et al showed that 80% of the patients with gallstone presented with other symptoms than biliary colic but the diagnostic rate of biliary colic had an increasing odds ratio in patients with gallstone disease.³³

Figure 5. Endoscopic Ultrasound of the Bile Ducts. Patient's permission.

The diagnostic method of choice to identify gallbladder stones is transabdominal ultrasound with a sensitivity and specificity of 95% of stones greater than 1.5 mm. Other modalities are MRCP or endoscopic ultrasound which are second line diagnostic procedures. MRCP is the primary procedure for diagnosis of common bile duct stones.³⁴ In patients with suspected complicated biliary disease, the overlap in diagnoses from the actual signs and symptoms are many. Computed Tomography (CT) can be a useful tool for these patients to rule out differential diagnoses, for example complicated disease originating from a suspected malignant lesion, for example acute cholecystitis with obstructive jaundice and a double duct sign on the CT (dilated ductus choledochus and ductus pancreaticus), or staging of an acute condition, i.e. perforation, abscesses, biliary obstruction level, Mirizzi syndrome, gallstone ileus, biliary pancreatitis etc. CT is also a very useful tool for evaluating postoperative conditions such as biliary leakage, drains, bleedings and iatrogenic perforations.³⁵ Low dose CT also provides the diagnostic tool of choice in an emergency setting with non-traumatic acute abdominal pain.³⁶



Figure 6. Compound crystallized Gallstone – with permission from the Patient
© Photo Siri Pålsson

1.3 RISK FACTORS

Gallstone disease is a high burden for western countries' health systems. Costs for treatment, including surgery are estimated to be \$4 – 6 billion USD annually calculated on 20.5 million affected inhabitants in the US between 20 - 74 years of age.^{37, 38}

Formation of gallstones is dependent of a series of complex interactions between diet,³⁹ genetic factors,⁴⁰ physical activity,⁴¹ and pathogenetic, hormonal and metabolic factors such as lipid homeostasis,⁴² female hormones,⁴³ and the metabolic syndrome.^{23, 44}

A recent meta-analysis based on prospective studies from Denmark with almost 3,000 participants and a mean follow up of 11.6 years with at least one re-examination for gallstone prevalence showed, that the only independent risk factors were female sex, BMI and non-HDL cholesterol – the same risk factors as for the metabolic syndrome. Self-rated health, lifestyle variables, blood pressure, alcohol consumption, smoking or triglycerides were not independent risk factors.⁴⁵

Other parameters that can influence the risk for gallstone disease are related to socioeconomic status.

Gender is a widely known risk factor and is believed to be due to the alterations in the composition in bile and stasis in the gallbladder secondary to oestrogen and progesterone secretion. The effect is dose-dependent and can be induced by pharmaceuticals. Gallstone disease is also associated with pregnancy and the risk itself increases with multiparity.^{30, 43}

Gallstone disease incidence increases with age and its presentation tends to differ between genders and amongst different ages. Women are more likely to experience biliary colic which is also the main surgical indication for women. Women also tend to undergo gallstone surgery in younger ages. For men the clinical presentation is more likely to be due to secondary complications to the disease and surgery is more likely to be performed in a later stage of life.³⁰ The difference in presentation may be secondary to the prevalence of gallstones which increases with age and the natural hormonal changes in women including pregnancies.

In Sweden the economic middleclass is large and the gaps in income and education are relatively small.⁴⁶ When looking at differences in how Sweden treats different socioeconomic subgroups with gallstone disease, there were no significant difference in regards to education, ethnicity and income.³⁰ In other countries, increased prevalence of gallstone disease has been associated with both high and low socioeconomic factors where obesity and dietary factors seem to be the common factors.⁴⁷

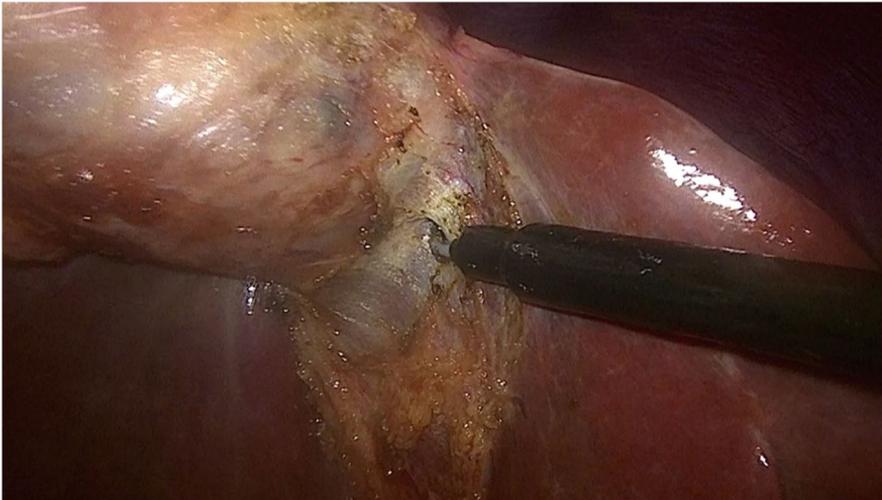


Figure 7. Removal of Vesica Fellea from Hepar. With permission from the patient.

1.4 PREVENTION

Different methods have been used to prevent gallstone disease. Examples include extracorporeal shockwave lithotripsy (ESWL), ursodeoxycholic acid, increased physical activity, coffee consumption, blood pressure monitoring, low-intake daily alcohol consumption and dietary changes.⁴⁴ Experimental therapy to stimulate gallbladder contraction and reduce the formation of gallstones such as electroacupuncture and how this treatment alters the gene expression in the gallbladder has also been studied in animal models⁴⁸. A few studies have been performed on Gut Microbiota. Patients with post cholecystectomy syndrome (p.13) have been examined with a control group by Georgescu et al where a correlation was found between gut dysbiosis and abdominal functional disorder such as bloating and pain. Wang et al discovered that certain bacteria such as Salmonella and Helicobacter pylori plays a role in the genesis of gallstones. The efficiency of antibiotics has not been evaluated. Di Ciaula et al found several pathogenetic factors involved in the gallstone genesis such as genetic alterations mimicking the mechanisms of the metabolic syndrome, gut microbiota and mobility changes in the bowel and the gallbladder. However it is not possible to withdraw any conclusions whether the genesis of the gallstones is affected by the altered microbiota per se or whether its alteration is an alternative clinical presentation of abdominal symptoms also existing in patients with asymptomatic gallstone disease.⁴⁹⁻⁵¹ Animal experiments on mice have shown that faecal transplantation from gallstone carrying mice to non-gallstone carrying mice can induce gallstone formation which supports the theory of the important role of gut microbiota in gallstone genesis.⁵²



Figure 8. No animal experiments were conducted during the research for this thesis

Ursodeoxycholic therapy, without or together with ESWL, has reported significant effect on reducing the risk for gallstone formation in high-risk patients without pre-existing gallstones, for example rapid weight loss, patients with gastric cancer undergoing gastrectomy and patients undergoing bariatric surgery. Current recommendations support limited use of ursodeoxycholic acid for high-risk subgroups to dissolve crystals.⁵³⁻⁵⁶ Another subgroup where ursodeoxycholic acid is used as prophylactic therapy is Cystic Fibrosis, however the quality of evidence for routine use ranges from very low to low.⁵⁷

Prophylactic cholecystectomy was generally recommended for asymptomatic gallstone disease until the French Consensus Conference on Cholelithiasis in 1991.⁵⁸ Systematic reviews based on retrospective cohort studies show no general benefit of surgery on asymptomatic gallstone carriers. But there is still debate on whether prophylactic cholecystectomy should be performed on some non-biliary surgical procedures, for example bariatric surgery, surgery in the young, patients with gastric cancer etc. Blinded, randomized, controlled trials are lacking, a situation that likely will remain due to ethical considerations, and the recommendation is not to perform prophylactic cholecystectomy on asymptomatic patients (Strength of recommendation C).⁵⁹⁻⁶³ One subgroup in which prophylactic cholecystectomy is recommended is patients with common bile duct stones. A systematic review evaluated the effect of prophylactic cholecystectomy in this subgroup compared with endoscopic sphincterotomy and the gallbladder left in situ with biliary colic or cholecystitis as endpoint. Prophylactic cholecystectomy was the therapy of choice since approximately 25% of those with deferral of cholecystectomy needed surgery at a later stage.⁶⁴

Post-cholecystectomy syndrome, i.e. persistent pain after removal of the gallbladder, is estimated to affect around 10% after surgery on patients with asymptomatic gallstone disease in a systematic review by Isherwood et al.⁶⁵ In patients with bariatric surgery, prophylactic cholecystectomy has been debated for many years and is recommended as a routine procedure due to the fact that almost 30% develop gallstones after surgery and over 50% of them get symptoms from their gallstones with potential complications.⁶⁶⁻⁶⁹ The reported improvement in quality of life after the combined procedure and an economic benefit also strengthen the indication – however the procedure is still controversial, and a recent meta-analysis shows that combining the procedure with cholecystectomy increases the risk of biliary complications and suggests

it should be avoided.⁷⁰ Prophylactic cholecystectomy is also currently recommended perioperatively in solid organ transplantations.⁷¹



Figure 9. The trajectory of gallstones passing to the duodenum

© Siri Pålsson with permission

1.5 TREATMENT

Treatment can be initiated for symptomatic gallstone disease such as biliary colic or for complicated disease as cholecystitis, common bile duct stones (CBD) with or without cholangitis, with or without obstructive jaundice and pancreatitis.

The treatment of choice is surgery, especially in cases of complicated disease with fever and leucocytosis, *cholecystitis acuta*. Cholelithiasis accounts for around 95% of all cases with acute cholecystitis and only 2% are spontaneously recovered within a course of two months. For patients suffering from previous attacks of biliary colic, the chance of reaching a state of asymptomatic disease for minimum 10 years ranges from 3 - 5%.⁷² Treatment is safe even for elderly >80 years of age, but careful selection of patients with comorbidity must be made. Independent factors increasing the mortality risk to be considered in this group are Charlson Comorbidity Score >2, open surgery and male gender.¹¹

In patients with CBD, endoscopic removal of the stones is the treatment of choice. Lee et al showed in a retrospective selected cohort study of patients with CBD that almost 20% needed a follow up cholecystectomy due to recurrence of symptoms from the gallbladder. In addition, if the patient suffers from pancreatitis or stones >10 mm size, they have independent risk factors for post-intervention cholecystectomy and are recommended to undergo a prophylactic intervention.⁷³

Laparoscopic cholecystectomy is the golden standard treatment if the surgeon and anaesthesiologist possess the necessary training and skills for the procedure. Laparoscopic surgery has a significantly lower number of complications, shorter hospital stay and lower mortality. The indications for open surgery is retained for patients with potential contraindications for laparoscopy, patients with suspected hepatobiliary malignancy and patients with advanced stage of inflammation and/or where the anatomy cannot be safely determined.⁷⁴

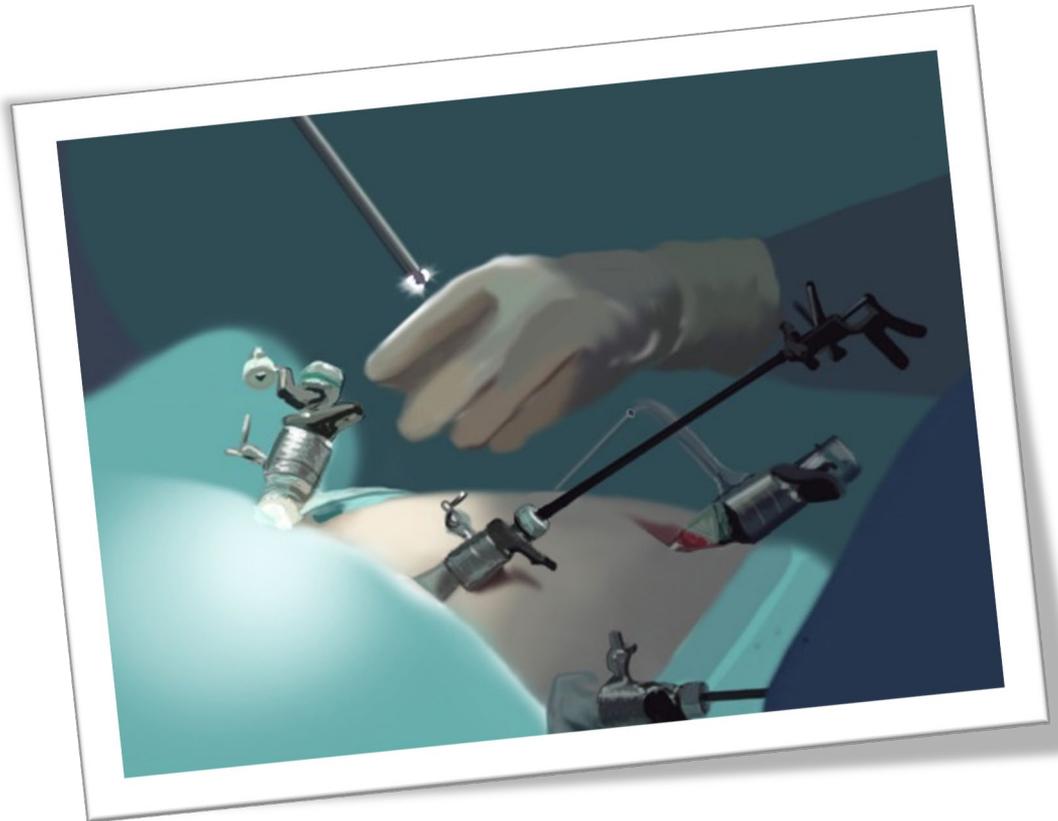


Figure 10. Illustration of a standard four-port laparoscopic Cholecystectomy setting. The surgeon is checking the light of the laparoscopic camera against the glove. The Umbilical port is for the camera. The epigastric and the high subcostal port are the operating ports. The lower right subcostal port is for the gallbladder grasper. The Gallbladder is extracted through the umbilical port.

© Siri Pålsson with permission

1.6 OUTCOME

Laparoscopic cholecystectomy (LC) has widened the indication for surgery and also increased the number of postoperative complications dramatically after its introduction and acceptance as first choice of treatment for symptomatic gallstone disease. Postoperative outcome after gallstone surgery can be measured as surgical complications such as mortality, morbidity, bile duct injury, wound infections, hernia, bleeding, gallbladder perforation, retained gallstones, bile leakage, iatrogenic bowel injury, incomplete or incorrect procedure due to anatomic uncertainties, induced common bile duct stones and conversion rate to open surgery; cardiovascular complications such as respiratory failure, myocardial infarction, arrhythmias, cardiac arrest, hospital related complications such as preoperative medication, opioid overdose, wrong preoperative diagnosis, malfunctioning equipment, forgotten equipment inside the patient, delayed procedure; follow-up with reduced quality-of-life, reduced patient experienced outcome and post-cholecystectomy syndrome with chronic pain.⁷⁵

To be able to improve the outcome after cholecystectomy it is of great importance to standardize how we are measuring our results, how we define complications, when we do follow ups and how we report different variables.

The overall objective of LC is to cure the patient from the gallstone disease with no sequelae, to restore quality of life and improve the patient reported outcome.

Alexander et al. reviewed 233 studies in 2018 to establish an overview in how complications are assessed and reported.⁷⁶

The authors showed that there was an inconsistency in how complications were defined, which parameters were registered as complications and grading on the severity of complications was missing in around 65% of the cases. Among the surgical units registering severity of the complications, formal classification systems were used by around 10%.

For common reported complications such as BDI and conversion to open surgery, the complication was found to be in 6% and 5% of cases respectively whereas 10 different definitions for BDI were reported from 13 different studies. Wound infections accounted for 16 different definitions.

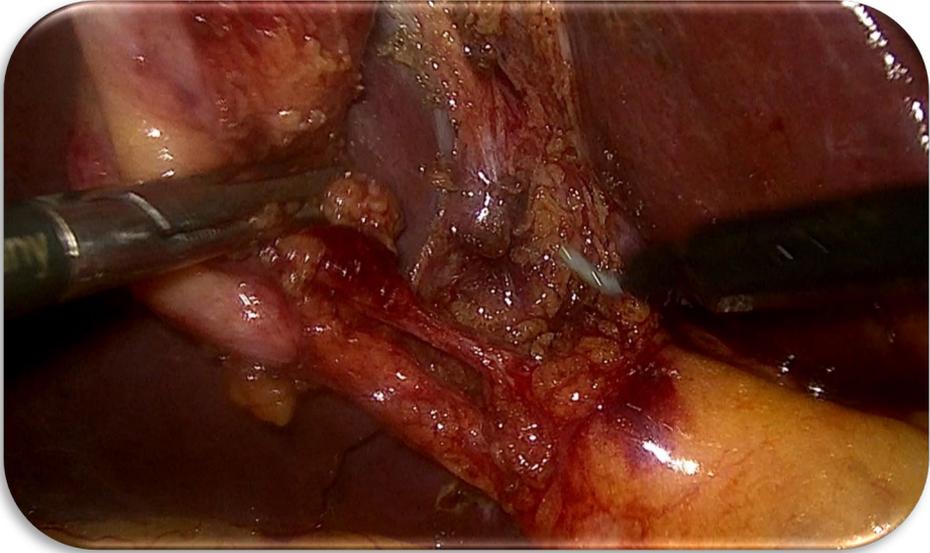


Figure 11. Critical view of Trigonum Cystohepaticum (Calot's Triangle). With patient's permission.

Health-related quality of life and Patient Reported Outcome have recently been gaining use when registering outcomes after surgery. The benefit of surgery for symptomatic patients. Patients with symptoms that undergo surgery, may experience a larger negative effect on quality of life than patients with little or no symptoms, where the risk of complications and postoperative pain triumph the potential advantages from the surgical intervention per se.⁷⁷ The definition of Quality of Life is not uniform and has interindividual differences. Quality of Life may also differ from Life Satisfaction. When using a formula for Quality of Life it is important to check how Quality of Life itself is defined and if that definition is suitable for its intended purpose, i.e. which domains are included, how different domains are described, how they are weighed towards one another and also that the formula is validated and reliable.⁷⁸⁻⁸⁰

Patient reported outcomes have been reported for many years both through disease specific and generic questionnaires. A few disease-specific

questionnaires for gallstones have been used constituting important instruments for completing a quality registration of the postoperative follow-up.⁸¹⁻⁸⁴

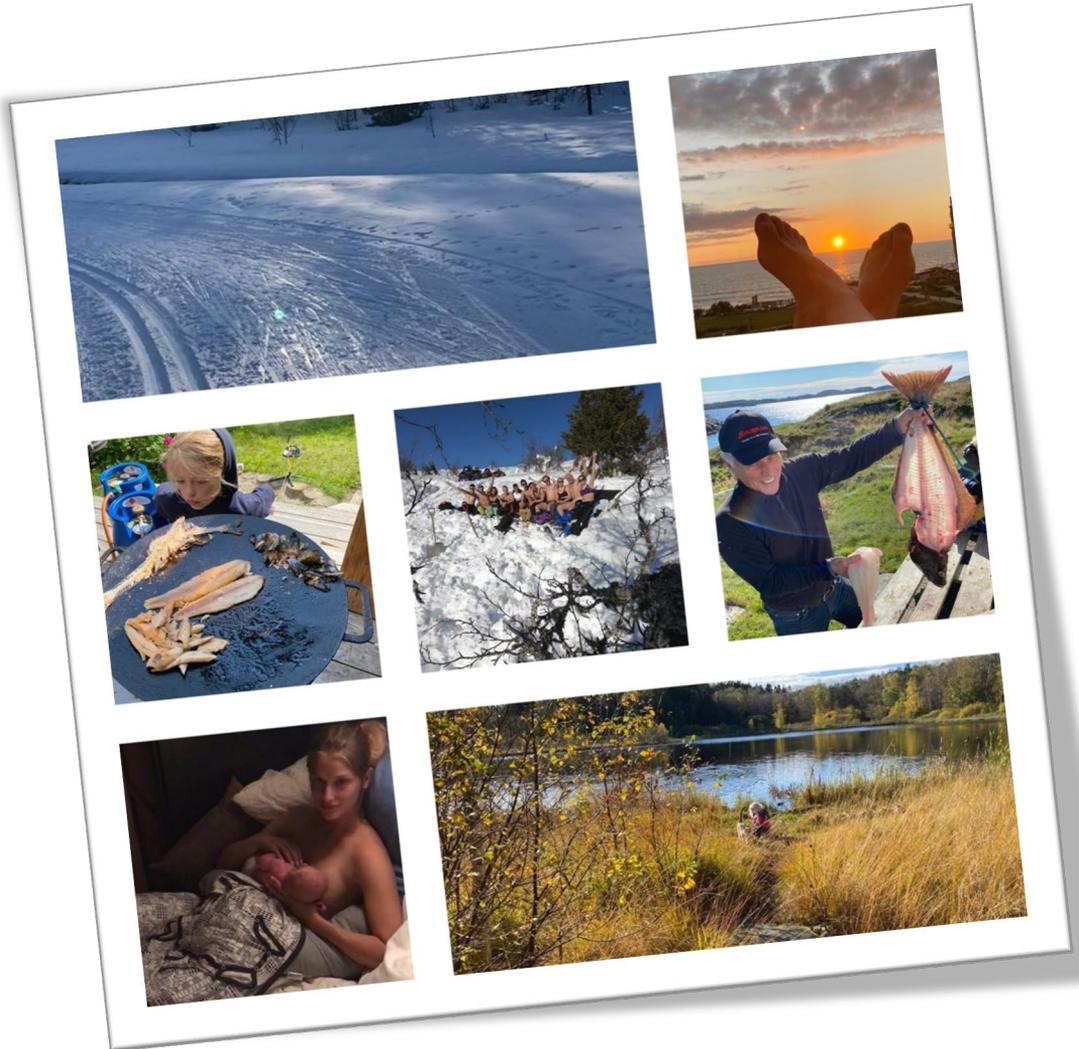


Figure 12. *Quality-of-life, or Life Satisfaction?*

©Photos: Private collection

The advantage with a disease specific formula is its potential greater sensitivity to detect the impact of an intervention. For all questionnaires measuring quality of life, it is important that they are constructed to maximise four main properties: sensitivity, validity, reliability and responsiveness. In other terms the questionnaire must be sensitive to the magnitude of real change, provide a valid measure of the concept investigated and to do so on each occasion the instrument is used. In addition, the instrument must also be responsive to clinically relevant changes. It must also answer the questions we are posing and changes in detected quality of life should correspond to an actual difference for the patient.

Many different QoL-formulas exist with different advantages and psychometric properties.⁷⁹ Generic quality of life formulas may be beneficial in a setting where comorbidities are expected and a more general view of the patients' quality of life is required. A generic formula also tends to be less sensitive to detect a change. Two general settings are described in the literature when it comes to quality-of-life instruments – discriminative, i.e. for cross sectional purposes and evaluative instruments for longitudinal purposes. For clinical trials the purpose of measuring quality of life can be to detect the effects of an intervention, for example in a randomised controlled trial where a need for a disease specific, sensitive scale with high responsiveness is preferred. In a longitudinal QoL questionnaire it is also important to have a high number of alternatives for the respondent on the questions to be able to describe and detect an actual change in QoL. Floor and ceiling effect are parameters to take into consideration in the interpretation of QoL results. If the responses generally are pointing at a very high or low tendency it is unlikely that the question has the possibility to have alternatives represented in the background population, hence less likely to detect a true change.^{79, 85}

In a clinical setting where a more general discrimination is wanted, a QoL formula with a cross sectional design can be chosen. A cross sectional formula is also preferable when less discrimination is needed between the answers and a fewer number of response alternatives are needed.

Psychometric properties differ between QoL formulas in terms of factor structure, item weighting, internal consistency, external (test-retest) reliability and validity against different instruments of known groups.

2 AIM

- To measure the patient experienced outcome and quality of life after gallstone surgery.
- To strengthen the decision basis of the surgeon
- To develop a disease specific questionnaire for measuring the patient-reported outcome.



Figure 13. High risk patient for developing cholesterol gallstone disease. Female, fertile around her forties, and overweight.

© Siri Pålsson with permission

3 MATERIALS AND METHODS

“Always be a little unexpected”

Oscar Wilde

3.1 REGISTERS



Since the initiation 17 years ago, Sweden has a national quality registry for gallstone surgery and ERCP. The initial aim with the registry was to improve quality and follow up and to obtain a national coverage to study treatments and results from gallstone-related interventions. The board of Gallriks consists of 12 surgeons appointed by the Swedish Surgical Society.

As of today, Gallriks covers >98% of the surgical units in Sweden and registers around 12,000 cholecystectomies annually.⁸⁶

All units registering in Gallriks are continuously evaluated and the information in the registry is counter checked against the patient journal. A conformity of >95% is mandatory.

Gallriks has national coverage since 2007. The registry contains information of the vast majority of cholecystectomies and Endoscopic Retrograde Pancreato-Cholangiographies (ERCP) performed in Sweden since 2005. Validation of the content in the registry shows a coherence of 97% between the information entered in Gallriks and the patient data. Procedures are registered perioperatively by the surgeon or the endoscopist. For cholecystectomies a 30-day and a 6-month follow up is registered. In addition, SF36 is registered pre- and 6 months postoperatively at selected units.

The first scientific study made from data on Gallriks was from 2010, and ever since a series of scientific papers and dissertations have been published based on its data.⁸⁷

Several studies have validated the registry which is a valuable source for data for routine follow up and scientific research.^{88, 89}

3.1.1 NPR

The National Patient Register (Swe: *Patientregistret*) is a mandatory register for all hospital inpatient care and outpatient visits to a specialist physician (excluding primary care) in Sweden. Its regulations are registered in the Swedish law (*Lagen om Hälso- och sjukvård 1998:543*) and governed by The Board of National Health and Welfare (Swe: *Socialstyrelsen*). Each registry has to include the patients' social security number (personal registration number), primary and relevant secondary diagnoses, treatment/measure, mechanism of injury when applicable, medical and administrative patient information. In 2020, 1,379,244 inpatient and 12,844,253 outpatient visits were registered. The register has national coverage since 1987.⁹⁰



Figure 14. Electrocardiogram. Open access

3.1.2 STATISTICS SWEDEN

Statistics Sweden, (Swe: *Statistiska Centralbyrån*)⁹¹ is a Swedish authority under the Department of Finance collecting official data that is published online to support research, national authorities and decision makers.

Statistics Sweden has 1,300 employees and an annual turnaround of 1 billion SEK. 50% of its turnaround is funded by the Swedish government.



Figure 15. Flash. Open access

3.1.3 CENTRAL DEATH REGISTER

The Central Death Register, CDR, (Swe: *Dödsorsaksregistret*)⁹² is a register for all deaths in Sweden and their cause. Children born dead are not included. The register is being updated one time per year. All information in the register is regulated by Swedish Law (*Begravningslagen* 1990:1144) and the register is being administrated by the National Board of Health and Welfare.

3.1.4 SWEDISH PRESCRIBED DRUG REGISTER

The Swedish Prescribed Drug Register, SPDR, (Swe: Nationella läkemedelslistan/former Läkemedelsföteckningen) is a register on an individual level on all drugs that have been distributed from pharmacies in Sweden. The register has been active since 2005 and is since 2021 held by E-hälsomyndigheten. The registered data is regulated by the Swedish Law (Lagen om Nationell Läkemedelslista 2018:1212).⁹³



Figure 16. Statistics. Open access

3.2 DESIGN

Papers I, II, III and IV are quantitative retrospective cohort studies and Paper V is a qualitative development of a questionnaire including focus group interviews, question reduction, statistical and psychometric analyses. Studies I-IV are based on national patient cohorts from Gallriks matched with the National Patient Register/Central Death register and Paper V is a preparation for a qualitative prospective study on a patient cohort from Gallriks.

- Paper I tested the responsiveness of SF36 on gallstone patients,
- Paper II investigated the influence of socioeconomic status on the decision to perform gallstone surgery,
- Paper III examined the safety of performing gallstone surgery on people over 80 years,
- Paper IV evaluated the risk factors for 30-day postoperative myocardial infarction after cholecystectomy and established a “safe period” of 8 weeks to avoid gallstone surgery after a previous myocardial infarction,
- Paper V is the first part of two in a study, where the first stage is a development of a disease generic PROM; The Gothenburg Gallstone Questionnaire (GGQ24). The second part is not included in this dissertation and will be the validation of the questionnaire. The first part is yet to be published.

Paper I

SF36, an 8-scale generic quality-of-life questionnaire, was administered pre- and 6-9 months postoperatively at a selected number of units performing acute and elective cholecystectomies and registered in Gallriks. Since an assessment of QoL of the Swedish background population with SF36 was previously performed, we could evaluate, how gallstone surgery has impact on the quality of life according to SF36 and evaluate if the SF36 was able to detect the impact of the intervention on HrQoL, i.e. its responsiveness for gallstone surgery. From the participating hospitals in the study, 817 patients underwent cholecystectomy during the collecting period.

Paper II

A retrospective register study was performed to assess the impact of socioeconomic background on decision making to undergo gallstone surgery. Socioeconomic data in Sweden was registered in Statistics Sweden, (Swe: Statistiska Centralbyrån).

All data from Gallriks between 2005 - 2009 was included in the study (39,333 interventions) and was crosslinked with Statistics Sweden. The incidence of surgery for patients undergoing cholecystectomy/100,000 inhabitants was, in regard to indication, calculated for data on income, education level, marital status, country of birth, age and gender.

Dichotomous variables were gender, country of birth (in Sweden/outside Sweden), marital status (married/not married), indication (biliary colic/cholecystitis pancreatitis or obstructive jaundice) and education level (equal or less than 9 years/ >9 years). Categorical variables were age, income (<median/2; median/2 – median; median – 2x median; >2x median). Multivariate regression analysis was performed.

Paper III

A retrospective cohort study of all patients registered in Gallriks over 80 years of age. Data from the procedure, indications, age, gender, operation method, conversion etc, was obtained from Gallriks.

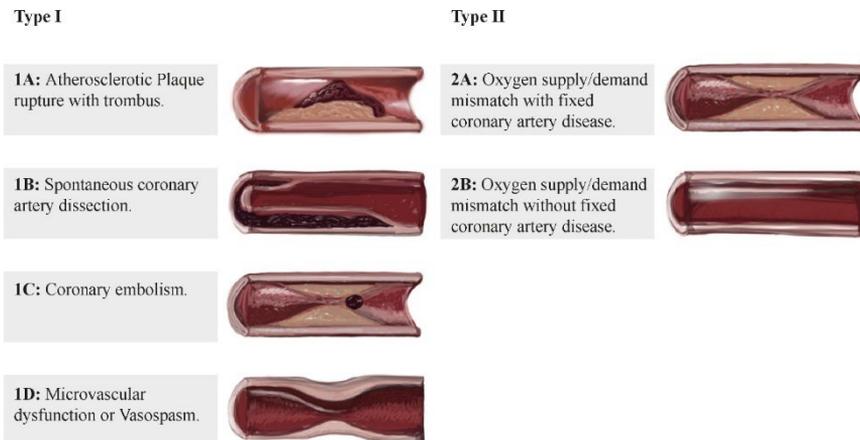
The endpoint for the study was a cardiovascular event within 30 days postoperatively. Out of 62,488 registered cholecystectomies, 1961 patients

were included in the study. Data was crosslinked with the Central Death Register by the National Registration Numbers to calculate a Standardised Mortality Ratio. Each patient was checked for comorbidities in the National Patient Register according to a previous validated routine using the National Registration Numbers and ICD-codes. Comorbidities were then calculated as a Charlson Comorbidity Score. Univariate and Multivariate analyses were performed.

Paper IV

A retrospective cohort study to assess the risk of postoperative MI following cholecystectomy. All data in Gallriks 2005 - 2014, 94,577 procedures on 31,068 men and 63,488 women with a mean age of 50, were included. The data were matched with the Swedish Inpatient Register (a part of the NPR) to obtain information about previous cardiovascular events. Information about medication was crosslinked with the Swedish Prescribed Drug Register were data regarding the use of drugs three months prior to the surgery was collected.

Vascular causes of Myocardial infarction.



Classification according to American Heart Association, de Lemos et al. 2019

Figure 17. Vascular causes of MI

© Illustration by Siri Pålsson with permission

Data regarding the procedure, patient data, ASA-score, BDI and complications was obtained from Gallriks. Data from the background population was obtained from Statistics Sweden. Multivariate regression analysis was performed. The endpoint was risk factors for 30-day postoperative myocardial infarction.

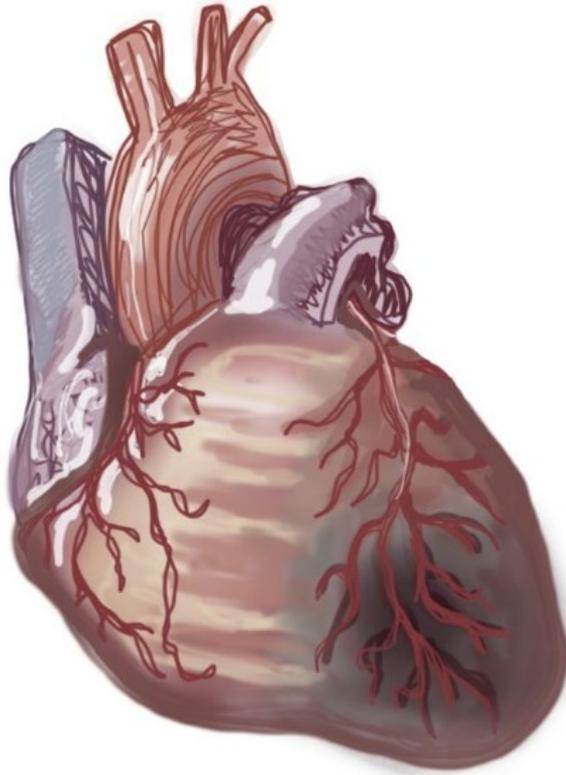


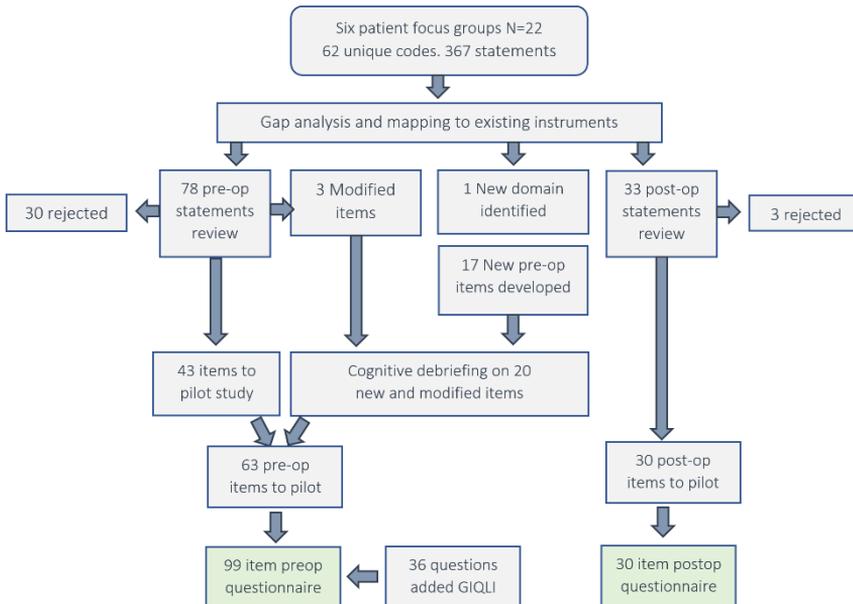
Figure 18. Cor. Myocardial infarction due to insufficient oxygen supply from *ramus interventricularis anterior arteriae coronariae sinistrae* (LAD)

©Siri Pålsson with permission

Paper V

Paper V consists of the first part of a larger prospective cohort study to establish the Patient Reported Outcome (PRO) after cholecystectomy in our own developed PROM formula – a disease specific self-reported formula covering both pre- and postoperative patients - The Gothenburg Gallstone Questionnaire (GGQ24). To develop the questionnaire, a mixed methods design was conducted with an existing generic questionnaire, PROMIS-items from question banks and existing forms. To develop new items, we used slightly altered guidelines from ISPOR's task force, Ad Modum Schifferdecker et al.⁹⁴ Focus group interviews were conducted with patients on the waiting lists for Surgery at two regional hospitals in southern Sweden. The questions were cognitively debriefed and condensed.

The transcripts were then coded and categorized in domains. Questions from validated PROMIS and GIQLI instruments were included. All focus group statements were thematically analysed by the research team. A medical expert team then reviewed the questions for comprehensiveness. Gap analysis was



Data was analyzed using IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp[27] and Stata[28].

Figure 19. Development of pilot questionnaires

performed, and all questions were mapped against GIQLI and PROMIS item banks. The pilot items were then cognitively debriefed with patients to identify ambiguity and comprehension.

Pilot items were then reviewed, changed, or dropped before two pilot questionnaires were developed, one for pre- and one for postoperative analysis.

The pilot questionnaires were distributed to patients pre- and postoperatively at five selected units in Sweden.

Psychometric and statistical evaluation was made with exploratory factor analysis, item analysis including internal consistency (Cronbachs α), ceiling and floor effects, and measures of symmetry (skewness). The item response model was used to define psychometric properties. Construct validity in relation to validated questionnaires followed by question reduction.

Finally poor functioning questions were eliminated, or the number of response alternatives were altered after visual analysis of the item characteristics curves.

4 RESULTS

- Petit à petit, l'oiseau fait son nid

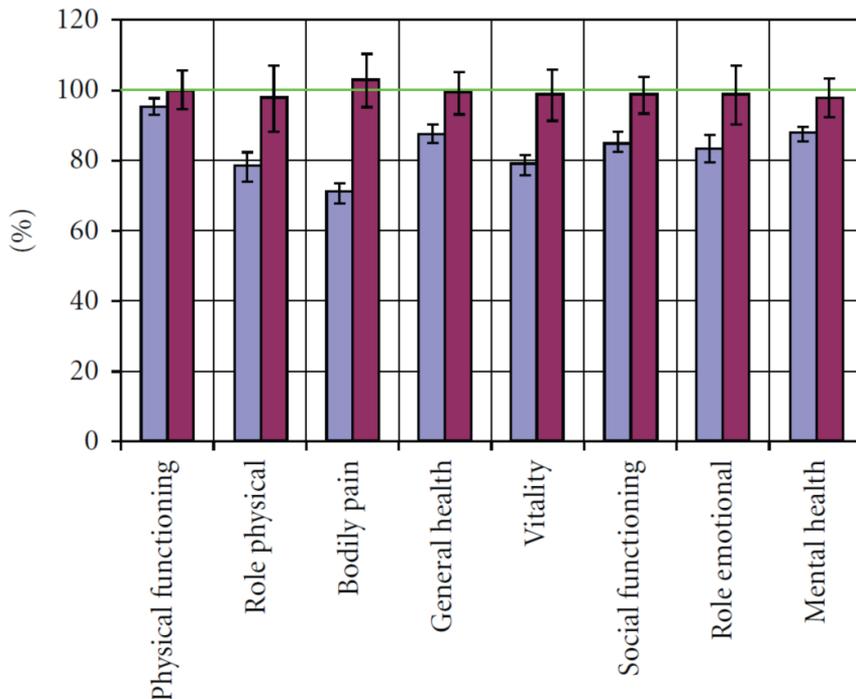
Per ardua ad astra

4.1 PAPER I

330 patients filled in the questionnaire prior to their intervention and 212 responded postoperatively. A total of 80 men and 250 women completed the survey with a mean age of 51 (SD 16).

Out of 542 respondents, 79.4% were operated on biliary colic as indication and 17.9% due to complicated gallstone disease. The majority was operated upon with laparoscopic approach (87.9%) compared to open or conversion which was 2.7 and 8.5% respectively. The subscales in SF36 were all equalled or exceeded 6 months after cholecystectomy with the largest effect on bodily pain. All domains showed a significant improvement.

Table 1.



Cholecystectomy proved to have a great intervention on the HrQoL and SF36 proved to have great responsiveness for measuring the effect on HrQoL after gallstone surgery. To measure the impact of the intervention, Standardised Response Means proved that the intervention has a large impact on bodily pain and a moderate effect on the physical component score.

Table 2.

Subscale	Standardized response mean	95% Confidence interval
Physical functioning	0.22	0.11–0.33
Role physical	0.49	0.37–0.61
Bodily pain	0.93	0.78–1.07
General Health	0.21	0.10–0.32
Vitality	0.38	0.26–0.50
Social Functioning	0.46	0.33–0.59
Role-emotional	0.31	0.18–0.45
Mental health	0.26	0.15–0.36
Physical component score	0.53	0.41–0.65
Mental component score	0.29	0.17–0.41

Evaluation of SRM [10]:

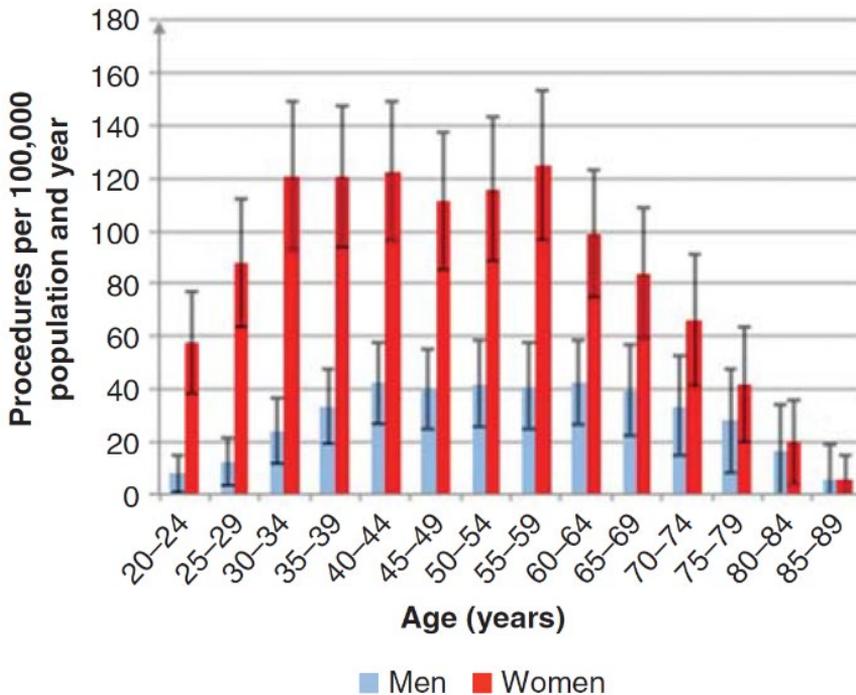
- (i) <0.20: trivial effect;
- (ii) 0.20–0.50: small effect;

4.2 PAPER II

In this large study material of 39,333 patients, 26,233 women and 12,839 men participated (271 not gender classified). The study revealed significant difference between men and women regarding the operation indication and the timepoint in life when surgery was performed. Undergoing gallstone surgery at high age had two independent predictors, male gender and complicated disease such as cholecystitis, obstructive jaundice or pancreatitis.

The presentation of the disease seems to differ, where women are more likely to get operated upon for the indication biliary colic at a younger age whereas men tend to undergo surgery later in life, and more often due to complications of the disease.

Table 3.



Socioeconomic variables included in this study do not have any significant impact on the decision to operate when a patient present with biliary colic or complicated gallstone disease.

4.3 PAPER III

62,488 cholecystectomies were registered in Gallriks during the years included in this study (2006 - 2011). 0.6% were excluded due to missing registration of age and/or gender. Gallriks' national coverage was over 90% during this period. In total 1072 women and 899 men qualified as octogenarians or nonagenarians with a mean age of 83 years. The oldest person included was 98 years of age.

Indication for surgery was:

- | | |
|------------------------------------|-------|
| • Colica biliara | 32.1% |
| • Cholecystitis acuta | 41.3% |
| • Cholecystitis chronica | 22.4% |
| • Pancreatitis acuta | 9.8% |
| • Obstructio ductus biliaris acuta | 18.6% |
| • Icterus (transiens) | 26.6% |

(Some patients had numerous indications for surgery)

Univariate analysis was performed where no factor turned out to have a significant prediction of a 30-day cardiovascular event. The risk for death however was independently associated with open surgery (excluding conversion from laparoscopic surgery), and operative indication biliary colic. Perioperative cardiovascular event was not run as a variable in the risk for death analysis, however it is likely it has a high 30-day postoperative mortality ratio in this age category.

Comorbidity with a Charlson Comorbidity Index >2 (n=197) was close to be significant (p=0.053) as an independent risk factor for mortality – the incidence in this group was 50% higher than in the lower Comorbidity index group.

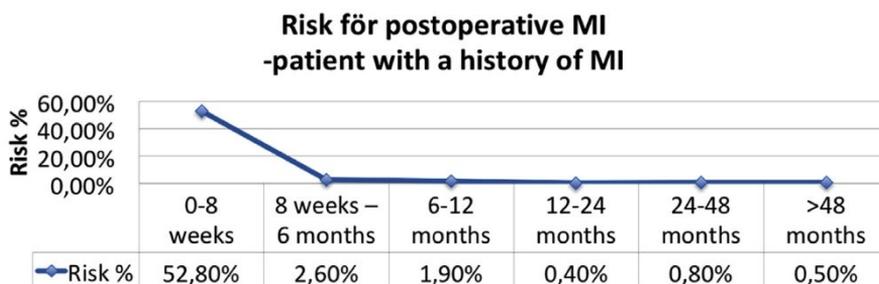
Postoperative care for patients undergoing laparoscopic surgery was 5 days shorter in average compared to open surgery (8,7 vs 2,7 days).

Surgery in this age group is relatively safe if careful preoperative selection is made.

4.4 PAPER IV

The odds ratio of having a 30-day postoperative MI was highest for those patients who underwent a preoperative NSTEMI. OR 11.98 (95%CI 7.10 – 20.28). The 95% CI is very wide due to a limited amount of data. The risk was highest (52.8%) for NSTEMI within 8 weeks prior to surgery. Independent risk factors were male gender, open approach, ASA class 3-5 and age >70 years. After 8 weeks the risk reduced with time.

Table 4.



The 30-day postoperative mortality was 0.2% in the group who did not suffer from a 30-day postoperative MI compared to 11.5% in the group who did.

Other complications as perioperative bleeding did not increase the risk for postoperative MI. 548 patients developed perioperative sepsis and suffered an increased risk of developing a perioperative MI (OR 2.89).

There was not any significant difference in use of Warfarin, ACE-inhibitors or Acetylsalicylic acid in the group affected by MI compared to those who did not.

Both the risk for 30-day mortality and 30-day postoperative MI was increased for the cohort undergoing cholecystectomy compared to the background population.

4.5 PAPER V

From the two participating hospitals' waiting list for cholecystectomy, six focus groups were conducted with a total of 22 patients. Three patients had already undergone surgery and the remaining 19 were still waiting. All chronic and transient indications for cholecystectomy were presented within the focus groups. The male:female ratio was 1:2.7 and the age distribution 32 - 81 years. All statements were coded according to the methods section and further analysis was made on their content. (Figure 3)

The pilot questionnaire was distributed to 600 pre- and 600 postoperative patients. The preoperative questionnaire contained 99 questions (including GIQLI) and the postoperative 30 questions. 17.3 and 28.2 % were returned with complete answers with a male female ratio of 1:2 and 1:1.2 respectively.

All questions were reviewed by the surgical team for clinical relevance.

After expert review, exploratory factor analysis, graded response model calibration and descriptive analysis, one domain and 75 questions could be discarded in the preoperative formula and 9 questions in the postoperative formula.

A disease specific PROM-formula was developed according to current scientific guidelines with a preoperative model of 24 questions and a postoperative model of 21 questions – The Gothenburg Gallstone Questionnaire (GGQ24). The questionnaire is yet to be validated.

Table 5.

GGQ24	Belly discomfort	Diet	Pain limitations	Social isolation	Sleep	Pain in the belly	Independence	Fatigue	Relationship to body
Belly discomfort	1,000								
Diet	0,497	1,000							
Pain limitations	0,721	0,383	1,000						
Social isolation	0,587	0,536	0,684	1,000					
Sleep	0,055	-0,034	0,142	-0,015	1,000				
Pain in the belly	0,484	0,365	0,698	0,601	-0,002	1,000			
Independence	-0,244	-0,171	-0,181	-0,355	0,229	-0,106	1,000		
Fatigue	0,698	0,432	0,665	0,672	-0,048	0,576	-0,214	1,000	
Relationship to body	-0,002	0,143	-0,026	0,184	0,201	0,045	-0,053	-0,122	1,000

Table 6.

GGQ24	GIQLI total	Physical	Bowel	Emotion	UpperG	Manage
Belly discomfort	0,802	0,698	0,555	0,610	0,810	-0,623
Diet	0,538	0,429	0,357	0,411	0,590	-0,373
Pain limitations	0,700	0,604	0,547	0,541	0,680	-0,559
Social isolation	0,748	0,644	0,567	0,579	0,684	-0,565
Sleep	0,056	0,050	0,000	0,020	0,041	0,026
Pain in the belly	0,592	0,509	0,324	0,481	0,566	-0,560
Independence	-0,268	-0,353	-0,160	-0,100	-0,242	0,164
Fatigue	0,667	0,573	0,519	0,485	0,634	-0,522
Relationship to body	0,208	0,224	0,041	0,150	0,083	0,047

5 DISCUSSION

The studies in this thesis show how gallstone surgery is practised in the community at large in Sweden. In each individual case, a careful trade-off between the potential hazards as well as benefits for the patients have to be considered before deciding on surgical treatment of the gallstone disease. In the absence of a reliable standard for weighing indications for surgery, it is difficult to reach equity and objective assessment of the indications for surgery. The GGQ 24 may be a tool that could aid in assessing the impact of the gallstone surgery on the population level.

Shared decision-making in surgery for benign conditions requires careful consideration of the potential hazards as well as assumed benefit from the procedure. Whereas gallstone surgery in general is considered as a procedure with little risk of adverse outcome, there is a small but not negligible risk of severe complications such as bile duct injury or cardiovascular complications. The benefit in terms of improved quality of life for the majority of patients undergoing surgery should thus be weighed against the risk of rare but severe events. This dilemma is even more pronounced in the elderly, since high age increases the risk of developing secondary complications to the gallstones, e.g., acute cholecystitis and biliary pancreatitis, as well as the risk of suffering cardiovascular complications following attempts to manage the gallstones surgically or endoscopically.

The previous and ongoing validation of the national register Gallriks was essential for this thesis. The access to national registers such as NPR, CDR, SS and SPDR were the key elements to get a national coverage and to verify the correctness of registered data. The external validity of the included studies is, to a great extent, dependent on the large amount of data collected in these registers and the ability to crosslink the information.

Performing register studies has many challenges where different types of biases must be considered. In all registers there is a risk that entered data is over or under interpreted and the cut-offs for different answers are set or interpreted differently. It is not unusual with a discrepancy between the medical record and the recorded truth.⁹⁵ There is also a risk that all patients or events are not registered which has been shown in previous investigations.^{96,97}

Studying quality of life is dependent on set criteria from the developer of the method used for evaluation. It is important to take into consideration that even if quality of life is improved in a certain subscale it might not be reflected in noticeably change in the life satisfaction of the patient.

The large impact of gallstone surgery on QoL seen in Paper I may partly be due to the placebo effect. No randomised double blinded trial has been performed comparing gallstone surgery with watchful waiting and is unlikely to ever take place due to ethical reasons and the effect of placebo is not known. The regression to the mean phenomenon is also important to take into consideration since some patients are likely to undergo surgery at a time point where their symptoms are at their worst and a natural decrease in symptoms would follow regardless of the surgical intervention. The impact of a surgical intervention is also affected by the preoperative state where patients with acute symptoms may experience a greater relieve than a patient with mild symptomatology.

Among the patients receiving the SF36 there were 36% non-responders. Since the data was compared with an age- and gender matched background population we do not know the health status in the non-responding group.

One limitation in this paper is that the PROM-formula used is not disease-specific. A generic questionnaire is less likely to detect change and less specific. Other symptoms not related to the gallstone disease per se may interfere. The strength of this paper is the high responsiveness of SF36 and that we can measure the impact of gallstone surgery on HrQoL with SF36.

Paper II was based on a very large study cohort which was cross linked with SS. When cross-linking the two registers, 7,772 (19.7%) of the posts were excluded in some of the subscales from SS. It is important to consider in a retrospective cohort that it is very difficult to track back in time how procedures were performed and how register was kept and there is a risk that data has been misinterpreted when entered into the register. Socioeconomic differences in both incidence and outcome have been previously reported for other types of surgery but was not detectable in our study.^{98, 99}

The difference between the number of procedures performed on women due to biliary colic may be secondary to the introduction of laparoscopic surgery and a shift of the indication – the interference of other gastrointestinal symptoms not originating from the gallstones also tend to be higher in this subgroup.¹⁰⁰ Our definitions of SES may prevent us from detecting any impact on

prevalence or outcome. High education on an individual may not be of importance for the socioeconomic status during childhood which may have affected the likelihood of developing a disease. Considering SES of the parents could give a different outcome than SES of the patients themselves. Income is also a continuous variable, where time as a covariable could have given a better selection of those suffering from low income during a longer period of time.

Paper II did not show an impact on outcome after surgery nor per- and postoperative complications for any of the socioeconomic subgroups. The strength of paper II is its large patient cohort and the ability to crosslink data with SS.

Among elderly, Paper II showed that there is a preponderance of men undergoing surgery at a later stage of life and more often secondary to complications of the disease. The subgroup “elderly” was less likely to undergo surgery, but the incidence of the gallstone disease increases with age.

The shift in indications for surgery caused by the lower threshold for laparoscopic surgery than for open surgery has also given a benefit for the elderly, with a significantly shorter postoperative hospital stay and lower mortality. Hence, Paper II focused on the safety on performing cholecystectomy on people aged 80 years or above. The limitation of Paper III is the small study cohort of 1961 individuals over 80 years of age, which may be the reason that we could not compare our data with any conservatively treated control group. The possibility to match the cohort to an age- and gender matched background population and the NPR is of great value for the study designs of Paper III and IV.

Cardiovascular events 30-day postop and mortality during the same period were both increased in the elderly, with a mortality rate four times higher than the background population. However, as a control group was lacking it is not possible to estimate the incidence in the event of conservative treatment for this group. The procedure was performed with an open approach on 4.3% in this population, which can contribute to a higher mortality as this has been shown to be an independent risk factor in Paper IV. A study from 2019 described surgery in the elderly more often being performed with traditional approaches. The fear of the physiological effect of laparoscopy on the intraabdominal pressure and cardiac output may be a reason that it is avoided to a larger extent in the elderly.¹⁰¹ Early studies also suggested that laparoscopic surgery would not provide any advantage over open surgery in complicated disease.¹⁰² However, more recent guidelines question the

conclusions from these studies and recommend laparoscopy even in the elderly for acute complicated disease.¹⁰³

Limitations in Paper III may be the cross-linking of different registers and how cardiovascular events were defined in the medical records and transcribed to diagnose codes. No independent risk factor could be shown for cardiovascular disease even though almost the same numbers were seen for mortality.

A surprising finding in Paper III was the fact that the mortality risk was higher in the subgroup operated upon for biliary colic than the group for acute complicated disease. This finding has not been duplicated in any other study and is regarded as selection bias.

Risk factors for postoperative myocardial infarction were assessed in Paper IV. Although postoperative myocardial infarction is a rare event following routine gallstone surgery, this risk has to be taken into consideration when deciding on surgery for a benign condition such as gallstone disease. The moderate benefit from alleviating gallstone symptoms from the majority of the population has to be weighed against the hazards of a myocardial infarction for a minority of the population.

The database covers all cholecystectomies performed in Sweden and is therefore representative for its standard population. The data on Myocardial infarct is entered from the inpatient register and it is possible that the strict criteria of an MI are not followed when the ICD code is entered in the data base. Both a false positive and a false negative incidence of a postoperative MI is possible.

The choice of dichotomous variables can give a skewed impression of the impact of a certain variable depending on where we choose to draw the cut-off. Regarding age, we first analysed age as a categorical variable and chose to draw the cut-off just below the variable with most impact, 70 years of age. Regarding BMI we wanted to know if there was any difference between people with overweight or no overweight and thus that cutoff was determined to 25.

The main variable was 30-day postoperative MI following cholecystectomy. 30-day postoperative complication (hypovolemic shock, septic shock, pulmonary embolism, stroke, wound rupture, multiorgan failure, reoperation) and indication for surgery are known predictors. A logistic regression model was built that showed a significant impact of the ASA-classification, the operation method, age, organ failure and previous MI on the 30-d-postoperative-MI as outcome.

A STEMI is an acute type 1 infarction and our data show that it is less dangerous with a previous STEMI than a NSTEMI. The explanation may be that a STEMI is treated with revascularization whether a NSTEMI is treated pharmacologically since a definitive measure don't has to be undertaken to protect the coronary vessel. It must be taken into account that there were only 9 Events Per Variable for STEMI so it is difficult to draw any definitive conclusion from such limited data. The postoperative complication variable was weighted with an OR of 3.34 (95% CI 1.95-5.74).

It was also significantly more hazardous to undergo open surgery or primarily laparoscopic surgery converted to open surgery. A conversion from laparoscopic to open surgery increases the odds of a postoperative MI with 224%. ASA classification >2 and age > 80 years old were also associated with higher odds. Postoperative complication was significant but did not have a major impact on the incidence of MI therefore it has not been reanalysed in split variables.

The odds of suffering a 30-day postoperative MI after gallstone surgery increased three-fold compared to the age- and gender matched background population. (Incidence in background population 2013 381/100,000 in 2013). These odds may appear unfavourable but are generally accepted due to the potential benefits of the intervention. Certain subgroups may face a considerably greater risk. The overall risk was independently increased by age >80 years, ASA classes 3–5, open cholecystectomy, laparoscopic surgery converted to open and a previous NSTEMI. Conversion from laparoscopic to open surgery was associated with a higher risk than an open procedure per se. History of a recent MI within 8 weeks prior to surgery was the greatest risk factor.

The incidence of postoperative MI after laparoscopy per se was 4% which is very close to the incidence of 3% in background population (Calculated from Statistics Sweden).

Similar results were shown in a Swiss register study of more than 22,000 patients. Increased perioperative risk for patients undergoing laparoscopic cholecystectomy was identified for male gender, age >70, ASA score 3 - 4, increased weight >90 kg, the surgeon's experience and complicated acute disease.¹⁰⁴

One of the most important aims of gallstone surgery is to provide relief from symptoms caused by the gallstones. Although this may seem as an obvious and uncomplicated issue, it may become very complex when attempting to define

all symptoms potentially associated with gallstones and the clinical importance of each individual symptom. Regardless of the characteristics, interference with the ability to undertake daily activities and specificity, all symptoms should be taken into consideration and weighed against the risk of being mistakenly assumed to be related to the gallstones when in fact being caused by other conditions. To better understand the impact of the interventions aimed at relieving gallstone symptoms, a PRO must be included as a standardized procedure in all surgery. To be able to detect change it is necessary with a disease specific instrument with high sensitivity.

Development of the GGQ24 incorporates the perspective of the patient's symptomatology in a healthcare system where the norm is usually set by the healthcare providers. Many patients undergo cholecystectomy for symptoms assumed to be related the gallstone when in fact they are related to functional disorders that may have great impact on QoL but are not permanently relieved by the cholecystectomy. The potential benefit of the intervention thus depends on whether it relieves the symptoms assumed to be caused by the gallstones.

GGQ24 is intended as a first step towards an instrument to evaluate the PRO between different units and to evaluate the impact of surgery on different subgroups.

There are, however, potential limitations of the validity of GGQ24. A relatively small pilot group completed the questionnaires, which may have affected the relevance of the IRT. All respondents received the questionnaire by post and may represent a selected subgroup in the background population. However, as various sources were used in the first selection process, the final version of the instrument may be assumed to be valid for all patients considered for gallstone surgery.

The next step is to test the GGQ24 in a prospective setting in a larger cohort to evaluate its ability to detect changes in quality of life. GallRiks provides a unique base for assessing the impact of gallstone surgery on the quality of life in a large population. GGQ24 is also intended for targeting specific research issues where the value of gallstone surgery is relevant.

5.1 ETHICS APPROVALS

Paper I -

Etikprövningskommittén i Stockholm (2008/43-31/4) Protokoll för signatur
EPN 2009/4:2

Paper II -

Etikprövningskommittén i Stockholm (2008/43-31/4) Protokoll för signatur
EPN 2010/5:6

Paper III -

Etikprövningskommittén i Stockholm (2012/164-31/3) Protokoll för signatur
EPN 2012/3:2.

Paper IV -

Etikprövningskommittén i Stockholm (2015/339-31/1) Protokoll för signatur
EPN 2015/1:3.

Paper V -

Etikprövningskommittén i Stockholm (2016/1438-31/4) Protokoll för
signatur EPN 2016/4:9.

6 CONCLUSION

- The impact of gallstone surgery can be measured with SF36 with good responsiveness. Bodily pain is the domain where surgery seems to have the greatest improvement. Cholecystectomy restores quality of life measured with SF36 to equal or exceed the one of the background population.
- In Sweden, neither the incidence nor outcome of gallstone surgery is affected by socioeconomic factors. Gallstone disease is presented differently in men and women. Also the indication for surgery and timing in life differs between the genders.
- Octogenarians or older may have great benefit from cholecystectomy – it can be a lifesaving procedure if surgery is performed after careful evaluation of the patient’s health status. Laparoscopic approach is recommended in this group as the first alternative; shorter hospital stay and lower mortality are important benefits.
- A previous Myocardial infarction is the strongest risk factor for a 30-day postoperative MI. The risk is highest after suffering from a non-revascularized infarction (NSTEMI) within 8 weeks before surgery. It also increased the mortality dramatically. Other complications increasing the risk independently was perioperative sepsis.
- Recent guidelines exist for how to create a PRO-measure with statistical and psychometric strengths. A disease-specific PROM was developed according to current guidelines with excellent psychometric properties, the GGQ24. The form will be validated in future research and its responsiveness will be examined.
- Gallriks and other Swedish registers contain large quantities of quality data and are reliable sources for research.

7 FUTURE PERSPECTIVES

Future research will address following subjects:

- Are there other means to measure the quality of surgery than patient registers and PRO-formulas?
- How do we get closer to differentiate the patients that will benefit from cholecystectomy from those who will not?
- Sweden is undergoing changes in its population and more polarisation of socioeconomic subgroups may arise due to immigration. How will this affect future decisions to perform cholecystectomy? Will the outcome be different in the future? Will other parameters differ between socioeconomic groups like the waiting time before getting surgery? Is the likelihood of undergoing surgery by a surgeon in training higher for certain subgroups? Does the outcome of surgery vary? How does the outcome in patient reported quality-of-life differ?
- Larger study material is needed to establish all independent risk factors for postoperative cardiovascular 30-day event.
- Will more careful preoperative selection of elderly increase survival? New studies with control groups with conservative treatment are needed.
- Will GGQ24 prove to be a valid formula with great responsiveness? How do the surgical care and treatment differ between operating units in Sweden?
- Will there be better tools for preoperative selection of patients suitable for surgery and shared decision-making?

ACKNOWLEDGEMENTS

I wish to express my sincerest gratitude to:

University of Gothenburg, Sahlgrenska Academy; represented by Professor **Peter Naredi**, Head of Department of the Institute of Clinical Sciences and Profestrix **Eva Angenete**, Head of the Department of Surgery, for giving me the opportunity to complete my PhD.

Lund University, at the time represented by Rector Emeritus Professor **Göran Bexell**, and its **Faculty of Medicine**, for giving me excellent training during my journey to complete my Medical Doctor degree.

Professor Associatus **Gabriel Sandblom**, my former main supervisor and co-supervisor, for limitless patience and support, a sharp mind and excellent scientific guidance.

Profestrix Associata **Cecilia Engström**, my main supervisor, for your devotion to teaching and supervising surgery, for treating me as if I was part of your family, for supporting me with your time during periods where you were overwhelmed with hard work, your big and caring heart and good advise.

Professor Associatus **John Chaplin**, for your friendship, patience, scientific skills and guidance within psychometric analyses.

Gallriks board – for all your hard work to keep a great national patient register in Sweden, and make it stay great.

Stefan Modin MD – my main supervisor through my Residency at Sahlgrenska, for your straight forwardness, your experience, and all tutorials with ambiance.

Professor **Hans Lönroth** and **Anders Rosemar MD, PhD**, for hiring me and believing in me.

Hans Axelsson MD, Mattias Block MD, PhD and **Dr Karin Sillén MD** for supervising me and giving me great responsibility during my early years in surgery training.

Professor **K.D. Boffard** for providing excellent Trauma Surgery training for me in Johannesburg.

All my **friends** and **colleagues** at the Sahlgrenska University Hospital for your patience, support, brilliance in wisdom and knowledge. In particular, but not limited to **Björn Holmström MD, Marta Berndsen MD, Emelie Larsson MD, Kaveh Khodakaram MD, Aiham Alaraj MD, Johan Tenser MD, Srdjan Kostic MD, Arild Saether MD, Nicke Antonov RN, Anahita Azhirnian MD, Maria Hermanson MD, PhD, Elham Sheikhan MD, Edvard Lecaros MD, Olöf Margrétardóttir MD and Karin Hedén MD** for great laughs, ice creams in the sun and for including me in your friendship.

Lunds Studentsångare, for all experiences, musical support and joy you have given me during med school that I will always carry with me.

Virum Plenum Fidei, for all adventures, endless friendship and being the greatest gentlemen, with extra thanks to my fellow student **Karim Saleh MD, PhD** for great proofreading.

Swedish Karate Kyokushinkai for always providing hard physical training, putting my mind at ease and teaching me self-control.

My dear **friends** and **family**, especially my little brother **Truls Pålsson, Reinklou family, Åström family, Johansson family, Knutsen family and my parents-in-law** for your unconditional love, amazing support, always being there, encouraging me, tolerating my periods of absence and being my safe haven.

My dear **father Göran Pålsson**, I feel your love and support. Thank you for opening all possibilities for me in life, for giving me freedom and love, for always believing in me and strengthening my weak sides. My **mother Greta Pålsson**, for teaching me manners, politeness, good behaviour and high moral values.

Stina & Lisa, my dearest amazing daughters – for your limitless energy, laughs and love. Thank you for keeping my feet on the ground and to prioritize what is important in life.

Siri Pålsson, my wife, the love of my life. Thank you for being smarter than me and for (almost) always being right. I love your brilliant thoughts and your logic, sharp mind. You are making me a better man.

I am grateful to the Gothenburg Medical Society and the Sahlgrenska University Hospital ALF agreement for financial support. In addition, I would like to thank the A. Ekman Foundation for their generous grant.

REFERENCES

1. Shehadi, W.H., *The biliary system through the ages*. Int Surg, 1979. **64**(6): p. 63-78.
2. Beal, J.M., *Historical perspective of gallstone disease*. Surg Gynecol Obstet, 1984. **158**(2): p. 181-9.
3. M, S., *The Classics of Medicine Library*. 1989.
4. Sims, M.J., *Cholecystotomy for the removal of gall-stones in dropsy of the gall-bladder*. 1878.
5. Langenbuch, C.J.A., *Chirurgie der Leber und Gallenblase*. Deutsche Chirurgie. Vol. 45. 1894-1897, Stuttgart, Germany: Verlag von Ferdinand Enke. 376pp.
6. van Gulik, T.M., *Langenbuch's cholecystectomy, once a remarkably controversial operation*. Neth J Surg, 1986. **38**(5): p. 138-41.
7. Reynolds, W., Jr., *The first laparoscopic cholecystectomy*. JSLs, 2001. **5**(1): p. 89-94.
8. Mouret, P., *How I developed laparoscopic cholecystectomy*. Ann Acad Med Singap, 1996. **25**(5): p. 744-7.
9. Sain, A.H., *Laparoscopic cholecystectomy is the current "gold standard" for the treatment of gallstone disease*. Ann Surg, 1996. **224**(5): p. 689-90.
10. Lord, A.C., et al., *Safety and outcomes of laparoscopic cholecystectomy in the extremely elderly: a systematic review and meta-analysis*. Acta Chir Belg, 2019. **119**(6): p. 349-356.
11. Palsson, S., G. Saliba, and G. Sandblom, *Outcome after cholecystectomy in the elderly: a population-based register study*. Scand J Gastroenterol, 2016. **51**(8): p. 974-8.
12. Tucker, J.J., et al., *Laparoscopic cholecystectomy is safe but underused in the elderly*. Am Surg, 2011. **77**(8): p. 1014-20.
13. Antoniou, S.A., et al., *Meta-analysis of laparoscopic vs open cholecystectomy in elderly patients*. World J Gastroenterol, 2014. **20**(46): p. 17626-34.
14. Arvidsson, D. and E. Gerdin, *Laparoscopic cholecystectomy during pregnancy*. Surg Laparosc Endosc, 1991. **1**(3): p. 193-4.
15. Enochsson, L., et al., *The Swedish Registry of Gallstone Surgery and Endoscopic Retrograde Cholangiopancreatography (GallRiks): A nationwide registry for quality assurance of gallstone surgery*. JAMA Surg, 2013. **148**(5): p. 471-8.

16. Ware, J.E., Jr. and C.D. Sherbourne, *The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection.* Med Care, 1992. **30**(6): p. 473-83.
17. PROMIS. *Instrument Development and Validation Scientific Standards Version 2.0 (revised May 2013)* Available from: https://www.mcgill.ca/can-pro-network/files/can-pro-network/promisstandards_vers2.0_final.pdf.
18. Admirand, W.H. and D.M. Small, *The physicochemical basis of cholesterol gallstone formation in man.* J Clin Invest, 1968. **47**(5): p. 1043-52.
19. Barbara, L., et al., *A population study on the prevalence of gallstone disease: the Sirmione Study.* Hepatology, 1987. **7**(5): p. 913-7.
20. Brazzelli, M., et al., *Systematic review of the clinical and cost effectiveness of cholecystectomy versus observation/conservative management for uncomplicated symptomatic gallstones or cholecystitis.* Surg Endosc, 2015. **29**(3): p. 637-47.
21. Muhrbeck, O. and J. Ahlberg, *Prevalence of gallstone disease in a Swedish population.* Scand J Gastroenterol, 1995. **30**(11): p. 1125-8.
22. Gutt, C., S. Schläfer, and F. Lammert, *The Treatment of Gallstone Disease.* Dtsch Arztebl Int, 2020. **117**(9): p. 148-158.
23. Portincasa, P., A. Moschetta, and G. Palasciano, *Cholesterol gallstone disease.* Lancet, 2006. **368**(9531): p. 230-9.
24. Borch, K., et al., *Prevalence of gallstone disease in a Swedish population sample. Relations to occupation, childbirth, health status, life style, medications, and blood lipids.* Scand J Gastroenterol, 1998. **33**(11): p. 1219-25.
25. Abou-Saif, A. and F.H. Al-Kawas, *Complications of gallstone disease: Mirizzi syndrome, cholecystocholedochal fistula, and gallstone ileus.* Am J Gastroenterol, 2002. **97**(2): p. 249-54.
26. Portincasa, P., et al., *Gallstone disease: Symptoms and diagnosis of gallbladder stones.* Best Pract Res Clin Gastroenterol, 2006. **20**(6): p. 1017-29.
27. Keulemans, Y.C., et al., *New strategies for the treatment of gallstone disease.* Scand J Gastroenterol Suppl, 2002(236): p. 87-90.
28. Jorgensen, T., *Abdominal symptoms and gallstone disease: an epidemiological investigation.* Hepatology, 1989. **9**(6): p. 856-60.
29. Wegge, C. and J. Kjaergaard, *Evaluation of symptoms and signs of gallstone disease in patients admitted with upper abdominal pain.* Scand J Gastroenterol, 1985. **20**(8): p. 933-6.

30. Palsson, S.H. and G. Sandblom, *Influence of gender and socioeconomic background on the decision to perform gallstone surgery: a population-based register study*. Scand J Gastroenterol, 2015. **50**(2): p. 211-6.
31. Festi, D., et al., *Clinical manifestations of gallstone disease: evidence from the multicenter Italian study on cholelithiasis (MICOL)*. Hepatology, 1999. **30**(4): p. 839-46.
32. Diehl, A.K., N.J. Sugarek, and K.H. Todd, *Clinical evaluation for gallstone disease: usefulness of symptoms and signs in diagnosis*. Am J Med, 1990. **89**(1): p. 29-33.
33. Berger, M.Y., et al., *Abdominal symptoms: do they predict gallstones? A systematic review*. Scand J Gastroenterol, 2000. **35**(1): p. 70-6.
34. Portincasa, P., et al., *Sonographic evaluation of gallstone burden in humans*. Ital J Gastroenterol, 1994. **26**(3): p. 141-4.
35. Patel, N.B., A. Oto, and S. Thomas, *Multidetector CT of emergent biliary pathologic conditions*. Radiographics, 2013. **33**(7): p. 1867-88.
36. Alshamari, M., et al., *Diagnostic accuracy of low-dose CT compared with abdominal radiography in non-traumatic acute abdominal pain: prospective study and systematic review*. Eur Radiol, 2016. **26**(6): p. 1766-74.
37. Sandler, R.S., et al., *The burden of selected digestive diseases in the United States*. Gastroenterology, 2002. **122**(5): p. 1500-11.
38. Everhart, J.E. and C.E. Ruhl, *Burden of digestive diseases in the United States Part III: Liver, biliary tract, and pancreas*. Gastroenterology, 2009. **136**(4): p. 1134-44.
39. Maclure, K.M., et al., *Weight, diet, and the risk of symptomatic gallstones in middle-aged women*. N Engl J Med, 1989. **321**(9): p. 563-9.
40. Attili, A.F., et al., *Prevalence of gallstone disease in first-degree relatives of patients with cholelithiasis*. World J Gastroenterol, 2005. **11**(41): p. 6508-11.
41. Ansari-Moghaddam, A., et al., *The Prevalence and Risk Factors of Gallstone Among Adults in South-East of Iran: A Population-Based Study*. Glob J Health Sci, 2015. **8**(4): p. 60-7.
42. Halldestam, I., E. Kullman, and K. Borch, *Incidence of and potential risk factors for gallstone disease in a general population sample*. Br J Surg, 2009. **96**(11): p. 1315-22.
43. Novacek, G., *Gender and gallstone disease*. Wien Med Wochenschr, 2006. **156**(19-20): p. 527-33.

44. Di Ciaula, A., et al., *The Role of Diet in the Pathogenesis of Cholesterol Gallstones*. *Curr Med Chem*, 2019. **26**(19): p. 3620-3638.
45. Shabanzadeh, D.M., L.T. Sørensen, and T. Jørgensen, *Determinants for gallstone formation - a new data cohort study and a systematic review with meta-analysis*. *Scand J Gastroenterol*, 2016. **51**(10): p. 1239-48.
46. *World Population Review Gini Coefficient*. 2022; Available from: <https://worldpopulationreview.com/country-rankings/gini-coefficient-by-country>.
47. Singh, V., et al., *Epidemiology of gallstone disease in Chandigarh: a community-based study*. *J Gastroenterol Hepatol*, 2001. **16**(5): p. 560-3.
48. Hao, M., et al., *RNA Sequencing Analysis of Gene Expression by Electroacupuncture in Guinea Pig Gallstone Models*. *Evid Based Complement Alternat Med*, 2022. **2022**: p. 3793946.
49. Georgescu, D., et al., *Dyspepsia and Gut Microbiota in Female Patients with Postcholecystectomy Syndrome*. *Int J Womens Health*, 2022. **14**: p. 41-56.
50. Di Ciaula, A., D.Q. Wang, and P. Portincasa, *An update on the pathogenesis of cholesterol gallstone disease*. *Curr Opin Gastroenterol*, 2018. **34**(2): p. 71-80.
51. Wang, Y., et al., *Role of the biliary microbiome in gallstone disease*. *Expert Rev Gastroenterol Hepatol*, 2018. **12**(12): p. 1193-1205.
52. Hu, H., et al., *Gut microbiota promotes cholesterol gallstone formation by modulating bile acid composition and biliary cholesterol secretion*. *Nat Commun*, 2022. **13**(1): p. 252.
53. Lee, S.H., et al., *Efficacy and Safety of Ursodeoxycholic Acid for the Prevention of Gallstone Formation After Gastrectomy in Patients With Gastric Cancer: The PEGASUS-D Randomized Clinical Trial*. *JAMA Surg*, 2020. **155**(8): p. 703-711.
54. Haal, S., et al., *Ursodeoxycholic acid for the prevention of symptomatic gallstone disease after bariatric surgery (UPGRADE): a multicentre, double-blind, randomised, placebo-controlled superiority trial*. *Lancet Gastroenterol Hepatol*, 2021. **6**(12): p. 993-1001.
55. Adams, L.B., et al., *Randomized, Prospective Comparison of Ursodeoxycholic Acid for the Prevention of Gallstones after Sleeve Gastrectomy*. *Obes Surg*, 2016. **26**(5): p. 990-4.

56. Talha, A., et al., *Cholelithiasis after bariatric surgery, incidence, and prophylaxis: randomized controlled trial*. *Surg Endosc*, 2020. **34**(12): p. 5331-5337.
57. Cheng, K., D. Ashby, and R.L. Smyth, *Ursodeoxycholic acid for cystic fibrosis-related liver disease*. *Cochrane Database Syst Rev*, 2017. **9**(9): p. Cd000222.
58. Cabarrou, P., G. Portier, and M. Chalret Du Rieu, *Prophylactic cholecystectomy during abdominal surgery*. *J Visc Surg*, 2013. **150**(4): p. 229-35.
59. Illige, M., A. Meyer, and F. Kovach, *Surgical treatment for asymptomatic cholelithiasis*. *Am Fam Physician*, 2014. **89**(6): p. 468-70.
60. Venneman, N.G. and K.J. van Erpecum, *Gallstone disease: Primary and secondary prevention*. *Best Pract Res Clin Gastroenterol*, 2006. **20**(6): p. 1063-73.
61. Gurusamy, K.S. and K. Samraj, *Cholecystectomy versus no cholecystectomy in patients with silent gallstones*. *Cochrane Database Syst Rev*, 2007(1): p. CD006230.
62. Sakorafas, G.H., D. Milingos, and G. Peros, *Asymptomatic cholelithiasis: is cholecystectomy really needed? A critical reappraisal 15 years after the introduction of laparoscopic cholecystectomy*. *Dig Dis Sci*, 2007. **52**(5): p. 1313-25.
63. Schmidt, M., et al., *A 24-year controlled follow-up of patients with silent gallstones showed no long-term risk of symptoms or adverse events leading to cholecystectomy*. *Scand J Gastroenterol*, 2011. **46**(7-8): p. 949-54.
64. McCarty, T.R., et al., *Role of Prophylactic Cholecystectomy After Endoscopic Sphincterotomy for Biliary Stone Disease: A Systematic Review and Meta-analysis*. *Ann Surg*, 2021. **273**(4): p. 667-675.
65. Isherwood, J., K. Oakland, and A. Khanna, *A systematic review of the aetiology and management of post cholecystectomy syndrome*. *Surgeon*, 2019. **17**(1): p. 33-42.
66. Bajardi, G., et al., *[Prophylactic cholecystectomy in bariatric surgery]*. *Minerva Chir*, 1993. **48**(6): p. 277-9.
67. Schirmer, B.D., K.L. Winters, and R.F. Edlich, *Cholelithiasis and cholecystitis*. *J Long Term Eff Med Implants*, 2005. **15**(3): p. 329-38.
68. Nagem, R. and A. Lázaro-da-Silva, *Cholecystolithiasis after gastric bypass: a clinical, biochemical, and ultrasonographic 3-year follow-up study*. *Obes Surg*, 2012. **22**(10): p. 1594-9.

69. Fobi, M., et al., *Prophylactic cholecystectomy with gastric bypass operation: incidence of gallbladder disease*. *Obes Surg*, 2002. **12**(3): p. 350-3.
70. Tustumi, F., et al., *Cholecystectomy in Patients Submitted to Bariatric Procedure: A Systematic Review and Meta-analysis*. *Obes Surg*, 2018. **28**(10): p. 3312-3320.
71. Kao, L.S., C. Flowers, and D.R. Flum, *Prophylactic cholecystectomy in transplant patients: a decision analysis*. *J Gastrointest Surg*, 2005. **9**(7): p. 965-72.
72. Tazuma, S., et al., *Evidence-based clinical practice guidelines for cholelithiasis 2016*. *J Gastroenterol*, 2017. **52**(3): p. 276-300.
73. Lee, K.M., et al., *Risk factors for cholecystectomy in patients with gallbladder stones after endoscopic clearance of common bile duct stones*. *Surg Endosc*, 2009. **23**(8): p. 1713-9.
74. Sun, S., et al., *Three-port versus four-port laparoscopic cholecystectomy: meta-analysis of randomized clinical trials*. *World J Surg*, 2009. **33**(9): p. 1904-8.
75. Veen, E.J., et al., *Outcome measurement in laparoscopic cholecystectomy by using a prospective complication registry: results of an audit*. *Int J Qual Health Care*, 2008. **20**(2): p. 144-51.
76. Alexander, H.C., et al., *Measurement of patient-reported outcomes after laparoscopic cholecystectomy: a systematic review*. *Surg Endosc*, 2019. **33**(7): p. 2061-2071.
77. Carraro, A., D.E. Mazloun, and F. Bihl, *Health-related quality of life outcomes after cholecystectomy*. *World J Gastroenterol*, 2011. **17**(45): p. 4945-51.
78. Gill, T.M. and A.R. Feinstein, *A critical appraisal of the quality of quality-of-life measurements*. *JAMA*, 1994. **272**(8): p. 619-26.
79. Hyland, M.E., *A brief guide to the selection of quality of life instrument*. *Health Qual Life Outcomes*, 2003. **1**: p. 24.
80. Landesman, S., *Quality of life and personal life satisfaction: definition and measurement issues*. *Ment Retard*, 1986. **24**(3): p. 141-3.
81. Russell, M.L., et al., *Disease-specific quality of life: the Gallstone Impact Checklist*. *Clin Invest Med*, 1996. **19**(6): p. 453-60.
82. Chen, T.Y., et al., *Questionnaire to aid priority and outcomes assessment in gallstone disease*. *ANZ J Surg*, 2006. **76**(7): p. 569-74.
83. Eypasch, E., et al., *Gastrointestinal Quality of Life Index: development, validation and application of a new instrument*. *Br J Surg*, 1995. **82**(2): p. 216-22.

84. Urbach, D.R., et al., *A measure of quality of life after abdominal surgery*. Qual Life Res, 2006. **15**(6): p. 1053-61.
85. Testa, M.A. and J.F. Nackley, *Methods for quality-of-life studies*. Annu Rev Public Health, 1994. **15**: p. 535-59.
86. Gallriks. *The Swedish National Register for Gallstone surgery and ERCP*. 2005; Available from: <https://www.ucr.uu.se/gallriks/>.
87. Enochsson, L., et al., *Nationwide, population-based data from 11,074 ERCP procedures from the Swedish Registry for Gallstone Surgery and ERCP*. Gastrointest Endosc, 2010. **72**(6): p. 1175-84, 1184 e1-3.
88. Rystedt, J., A. Montgomery, and G. Persson, *Completeness and correctness of cholecystectomy data in a national register--GallRiks*. Scand J Surg, 2014. **103**(4): p. 237-44.
89. Enochsson, L., et al., [*GallRiks 10 years. Quality registry for gallstone surgery have improved health care*]. Lakartidningen, 2015. **112**.
90. Welfare, T.N.B.o.H.a. *National Patient Register*. 1987; Available from: <https://www.socialstyrelsen.se/statistik-och-data/register/patientregistret/>.
91. SCB, S. *Statistiska Centralbyrån*. Available from: <http://scb.se>.
92. Registry, C.D. *The National Board of Health and Welfare*. Available from: <https://www.socialstyrelsen.se/statistik-och-data/register/dodsorsaksregistret/>.
93. E-hälsomyndigheten. *Nationella läkemedelslistan*. 2021; Available from: <https://www.ehalsomyndigheten.se/tjanster/yrkesverksam/nationella-lakemedelslistan/>.
94. Schifferdecker, K.E., et al., *A method to create a standardized generic and condition-specific patient-reported outcome measure for patient care and healthcare improvement*. Qual Life Res, 2018. **27**(2): p. 367-378.
95. Wauben, L.S., et al., *Operative notes do not reflect reality in laparoscopic cholecystectomy*. Br J Surg, 2011. **98**(10): p. 1431-6.
96. Elfstrom, J., A. Stubberod, and T. Troeng, *Patients not included in medical audit have a worse outcome than those included*. Int J Qual Health Care, 1996. **8**(2): p. 153-7.
97. Dreisler, E., L. Schou, and S. Adamsen, *Completeness and accuracy of voluntary reporting to a national case registry of laparoscopic cholecystectomy*. Int J Qual Health Care, 2001. **13**(1): p. 51-5.

98. Krupic, F., et al., *Influence of ethnicity and socioeconomic factors on outcome after total hip replacement*. Scand J Caring Sci, 2013. **27**(1): p. 139-46.
99. El-Sayed, A.M., et al., *Insurance status and inequalities in outcomes after neurosurgery*. World Neurosurg, 2011. **76**(5): p. 459-66.
100. Bianchi, M.T., M. Lattanzi, and C. Zimmermann-Tansella, *Psychosocial factors in women who undergo cholecystectomy. A case-control study*. Psychopathology, 1989. **22**(6): p. 335-43.
101. Scandrett, K.G., B.S. Zuckerbraun, and A.B. Peitzman, *Operative risk stratification in the older adult*. Surg Clin North Am, 2015. **95**(1): p. 149-72.
102. Uecker, J., et al., *Cholecystitis in the octogenarian: is laparoscopic cholecystectomy the best approach?* Am Surg, 2001. **67**(7): p. 637-40.
103. Pisano, M., et al., *2017 WSES and SICG guidelines on acute calculous cholecystitis in elderly population*. World J Emerg Surg, 2019. **14**: p. 10.
104. Giger, U.F., et al., *Risk factors for perioperative complications in patients undergoing laparoscopic cholecystectomy: analysis of 22,953 consecutive cases from the Swiss Association of Laparoscopic and Thoracoscopic Surgery database*. J Am Coll Surg, 2006. **203**(5): p. 723-8.