Gallstones

NO STONE LEFT UNTURNED



F.M. Thunnissen

Stellingen behorende bij het proefschrift

GALLSTONES

No Stone Left Unturned

1. De keuze voor een cholecystectomie wordt al in de eerste lijn gevormd.

2. Galstenen op de echo zijn een bevinding, geen verklaring.

3. Primair gecompliceerd galsteenlijden vraagt om vroege risico-opsporing, niet om een lagere operatiedrempel op de polikliniek.

4. Een cholecystectomie is geen placebo, maar het placebo-effect ervan is groter dan we denken.

5. De selectie van patiënten voor een operatie is de belangrijkste factor voor het behalen van de ideale uitkomst.

6. Een ongecompliceerde operatie is geen garantie voor een succesvolle behandeling.

7. Als patiënten na een keuzehulp krijgen wat ze willen, wil dat niet altijd zeggen dat ze krijgen wat ze nodig hebben.

8. Een keuzehulp verplaatst een deel van het consult van informatieoverdracht naar gezamenlijke besluitvorming.

9. “Soms denk ik uren na en heb ik nog niks op papier, een andere keer bereik ik precies datzelfde in vijf minuten.” – *Herman Finkers*

10. “No matter where life takes me, find me with a smile.” – *Malcolm James McCormick (Mac Miller)*

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Floris Martijn Thunnissen

2026

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Layout and cover design: WAUD
Printing: ProefschriftMaken || www.proefschriftmaken.nl

Gallstones
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Proefschrift ter verkrijging van de graad van doctor
aan de Radboud Universiteit Nijmegen
op gezag van de rector magnificus prof. dr. J.M. Sanders,
volgens besluit van het college voor promoties
in het openbaar te verdedigen op

vrijdag 27 november 2026
om 12.30 uur precies

door

Floris Martijn Thunnissen
geboren op 13 juli 1994
te Utrecht

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CHAPTER

1

GENERAL INTRODUCTION

GALLSTONE DISEASE

For decades, medical students have learned a mnemonic to memorize people at risk for gallstones, *the four F's*: Female, Fat, Forty and Fertile. (1) Nowadays, most of these risk factors are still recognized with the addition of more general factors such as older age, physical inactivity and obesity, but also the role of genetics. (2, 3) Bile is produced by the liver and collected in the gallbladder. The gallbladder stores bile acids, concentrates them in micelles and, after the consumption of food, regulates the release of gall into the duodenum to help digest and absorb fats. (4, 5) In 15-20% of the general population, however, gallstones form in the gallbladder or biliary tract. (2)

Notably, most gallstones remain asymptomatic, but every year 2-4% of people with gallstones develop symptoms. (6-8) The most frequent symptom is a biliary colic, which is defined as a severe pain attack, located in the upper or upper-right abdomen, lasting for fifteen minutes or more. (9) A biliary colic is often referred to as symptomatic uncomplicated gallstone disease. In addition, gallstones may lead to biliary complications, such as cholecystitis, choledocholithiasis, biliary pancreatitis or cholangitis. In the Netherlands, the annual incidence of patients with gallstones presenting at the hospital rises, from 30 000 in 2012 to 37 000 in 2022 (Fig. 1). (10) The gold standard treatment for uncomplicated gallstone disease is a laparoscopic cholecystectomy, mainly for pain-relief and to prevent biliary complications. In the Netherlands, roughly 24 000 cholecystectomies are performed annually (Fig. 1). Generally, there is a clear indication for removal of the gallbladder by laparoscopic cholecystectomy in the case of complicated gallstone disease (e.g. cholecystitis, biliary pancreatitis). (11-13)

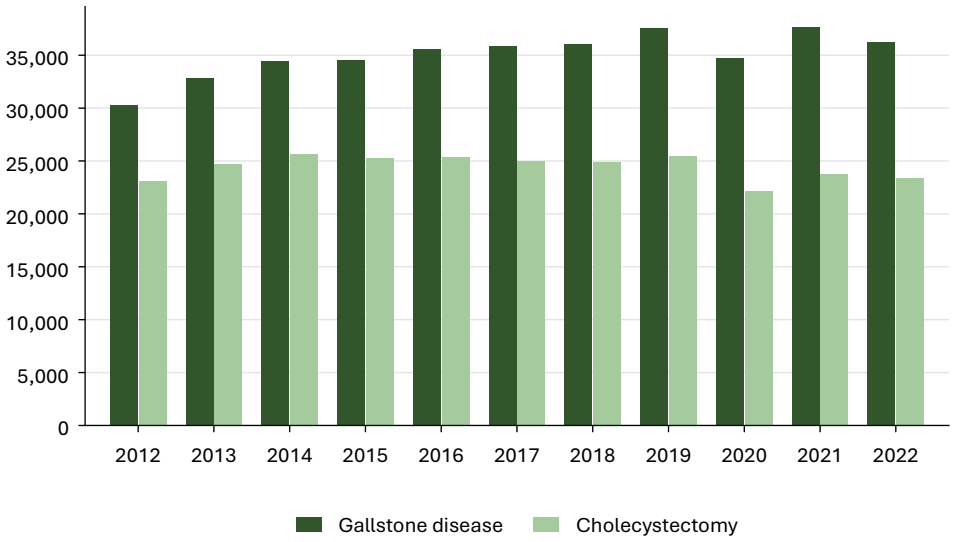

Figure 1, The annual incidence of gallstone disease in Dutch hospitals and the number of cholecystectomies performed

Conversely, the indication for cholecystectomy in the case of uncomplicated gallstone disease is not as evident. (2, 6, 13, 14) In recent years, the value of biliary colic as an indication for cholecystectomy is contested, as up to 40% of patients still experience abdominal pain after surgery. (15-18) This outcome questions whether gallstones were the cause of abdominal pain in the first place, or that the presence of gallstones may have been incidental in combination with other causes of pain. Particularly in this group of patients watchful waiting could be a more appropriate approach.

The potential risks of conservative treatment and the risk of recurrent biliary colic and biliary complications, must also be weighed against the risks of surgery. Besides general surgical complications, such as wound infections and bleedings, the most important and disabling complication to consider is bile duct injury, which occurs in 0.19-1.5% of cholecystectomies. (19-21)

QUALITY AND OUTCOME ASSESSMENT OF GALLBLADDER SURGERY

Gallstone disease is commonly evaluated using single outcome parameters, such as abdominal pain or technically flawless cholecystectomy. (15-18) However, this approach

does not do justice to the complexity of reality. Many patients with gallstones often suffer from other concomitant abdominal symptoms like functional dyspepsia or irritable bowel syndrome. (22, 23) These syndromes may also cause abdominal discomfort and pain and thereby cause confounding in the reported outcomes. Moreover, other desirable and undesirable outcomes may occur in patients with gallstones or during treatment for symptomatic gallstone disease. The outcomes include biliary complications, surgical complications associated with cholecystectomy, side-effects of medication and new symptoms due resulting from cholecystectomy. (24-26) Next to clinical events, patients' subjective experiences with care are important in defining successful treatment, but are often overlooked. (27) Generally, evaluation of treatment has often been one-dimensional and approached from a surgical perspective, but failed to incorporate the patients' perspectives. This highlights the need for a broader framework to assess and benchmark treatment success in gallstone disease.

CLINICAL PATHWAY AND SHARED DECISION-MAKING

In the Netherlands, essentially all patients undergo initial evaluation by their primary care physician before being referred to the outpatient clinic or emergency department at the hospital. This accentuates the role of the general practitioner in the treatment of patients with symptomatic gallstone disease. Studies regarding the management of gallstone disease in primary care are limited, because the bulk of research is performed in secondary care. (28) The role of the general practitioner in the clinical pathway of patients with upper abdominal pain, and the circumstances under which they decide to refer a patient to the hospital are largely unidentified.

Additionally, general practitioners can request a non-invasive tool for the detection of gallstones: the abdominal ultrasound. (29) Both specificity and sensitivity are high for the detection of gallstones (95% and 97%, respectively). (30) The accessibility of an ultrasound contributes to its frequent utilization in patients with upper abdominal pain, but the expediency and diagnostic yield in the light of the disputable diagnosis of gallstone disease are less known.

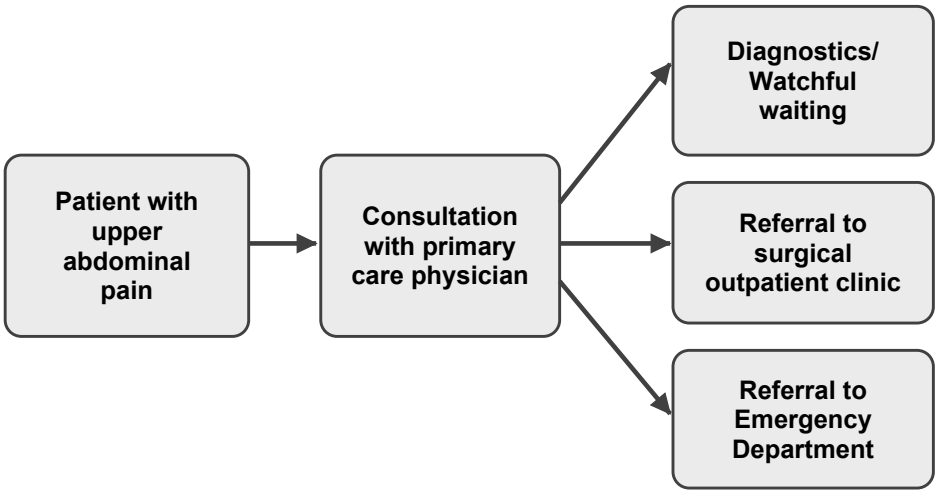

Figure 2, Common clinical pathway of a patient with upper abdominal pain in the Netherlands

THE USE OF DECISION AIDS

In recent decades, the relationship between physician and patient has changed from a paternalistic approach into a collaborative decision-making process, often termed *Shared decision-making (SDM)*. (31) During this process, the best available evidence is balanced with the patients' preferences to come to a decision for treatment. This may lead to more appropriate care and has been shown to reduce surgery rates. (32) Given the indeterminate outcomes after cholecystectomy and the viable option of watchful waiting for patients with uncomplicated gallstone disease, it can be a staple disease for SDM.

A relatively new manner of applying SDM is with the use of decision aids. Decision aids are tools to improve disease specific knowledge of patients, inform on possible treatment options and incorporate personal values in treatment decision. Better-informed patients are able to make better value-congruent choices and have less decisional-conflict. (33, 34) Some research has also shown that SDM with or without decision aids may lead to more conservative choices of treatment. (33, 35) Nevertheless, the effect of decisions aids on surgery rates and patient-reported outcomes for surgical procedures is scarcely researched.

Although gallstone disease is common, little is known about how patients with suspected gallstone disease are managed and how diagnostic imaging is utilized in primary care. In addition, outcomes of patients with gallstone disease are insufficiently under-

stood, and there is no consensus on what constitutes successful treatment, particularly from a patient-centered perspective. Finally, elective surgery for gallstone disease is preference-sensitive, yet insight into the use and impact of shared decision-making and decision aids remains incomplete.

AIM OF THE THESIS

The aim of this thesis was to see further than the pure technical treatment of gallstone disease by surgeons in secondary care. There were three main research themes:

- To optimize the clinical pathway for patients with suspected symptomatic gallstone disease, with a focus on diagnostic accuracy, patient selection, and shared decision-making.
- To identify which outcomes meaningfully define successful treatment of uncomplicated gallstone disease and to develop valid methods for measuring these outcomes.
- To evaluate the contribution of shared decision-making and decision aids to treatment choice and patient-reported outcomes in elective surgical care, including cholecystectomy.

To answer these questions, the following studies were performed: one mixed-method study, three prospective cohort studies, three retrospective cohort studies and one post-hoc analysis of 2 prospective trials. Furthermore, I coordinated one multicenter trial with a stepped-wedge design, of which the protocol is included in *Part III*.

OUTLINE OF THE THESIS

This thesis consists of three parts. The first part investigates the clinical pathway and outcomes of patients with gallstone disease in both primary and secondary care, while the second part delves into how success in treatment of gallstone disease should be measured and the third part explores the role of shared decision-making in surgery.

Part I – Treatment Outcomes in Gallstone Disease

Chapter 2 provides an insight in the treatment of gallstone disease by the general practitioner. We report on healthcare utilization in the years before and after the diagnosis of gallstone disease and show the complexity of treating patients with upper abdominal pain. In Chapter 3, we evaluate the yield of referrals for an ultrasound by the general practitioner in patients with the suspicion of symptomatic gallstone disease. Moreover, we develop a multivariable prediction model to assist general practitioners in the selection of patients for an abdominal ultrasound.

Chapter 4 was executed during the SARS-CoV-2 pandemic. During this pandemic, elective surgeries were postponed considerably or even cancelled. These circumstances enabled us to investigate the effects of restricted healthcare access on elective surgeries in terms of disease-related complications in patients with gallstone disease or an inguinal hernia. This may help to substantiate watchful waiting as a viable option.

In Chapter 5, we investigate which abdominal complaints patients experience after cholecystectomy. Questionnaires were filled out by patients before and after surgery to establish which symptoms can successfully be addressed through cholecystectomy, but also which complaints might be triggered as a consequence of gallbladder-removal. This helps to accurately inform patients on the results of cholecystectomy.

Part II – Revisiting the Assessment of Outcomes in Gallstone Disease

Chapter 6 converses on the ideal- or *Textbook outcome* we should strive for in patients with uncomplicated symptomatic gallstone disease. In this mixed-method study, we conduct focus groups with physicians and patients, survey surgeons and gastroenterologists from 81 different countries, and eventually define an international consensus-based textbook outcome. This composite outcome can be used for quality-assurance and research purposes. The subsequent Chapter 7 explores factors that are associated with this novel textbook outcome.

In Chapter 8, the development and validation of a new health-related quality of life questionnaire for patients with symptomatic gallstone disease is described, the Gall-Q. Unlike other questionnaires that are currently being used, the Gall-Q is developed specifically for patients with gallstone disease and more concise. This facilitates the use of patient-reported outcomes in the clinical setting.

Part III – Shared decision-making

Chapter 9 is the study protocol of the E-valuAID study. This multicenter study with a stepped-wedge design answers the question whether shared decision-making with the help of decision aids for elective surgery may reduce surgery rates, while also improving patient-reported outcomes. This study considers the four most commonly performed general- and orthopedic surgeries: cholecystectomy, inguinal hernia repair, knee- and hip replacement.

In Chapter 10, the use of decision aids is retrospectively examined. We report on the correlation between patients' expressed preferences and received treatment. Furthermore, we analyze which patient values and clinical factors are associated with the decision for surgery.

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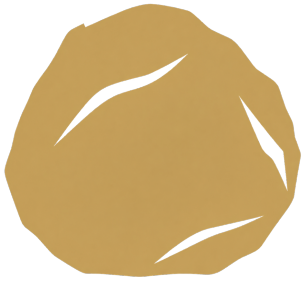
PART I

Treatment Outcomes in Gallstone Disease





CHAPTER

2

Healthcare utilization of patients with cholecystolithiasis in primary care. A multi-practice comparative analysis.

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BMJ Open 2021

ABSTRACT

OBJECTIVES To examine general practitioners' (GP) management of cholecystolithiasis and to evaluate persisting abdominal complaints in the years after the diagnosis.

DESIGN Retrospective analysis of registry data and a subset of individual medical records

SETTING Seventeen primary care practices affiliated with the Radboudumc Practice Based Research Network in the Netherlands.

PARTICIPANTS 633 patients with cholecystolithiasis diagnosed between 2012-2016.

PRIMARY AND SECONDARY OUTCOME MEASURES The primary outcome of this study was the healthcare utilization of patients with cholecystolithiasis diagnosed by the GP in terms of referrals to secondary care, laboratory diagnostics, prescribed medication, and the prevalence of concomitant abdominal-related diagnoses in a time interval of 3 years before and 3 years after diagnosis of cholecystolithiasis. For secondary outcomes, Electronic Medical Records were studies from seven practices to assess emergency department visits, operation rates and repeat visits for persistent abdominal symptoms. We compared the non-referred group with the referred group.

RESULTS In 57% of patients, concomitant abdominal-related diagnoses were recorded besides the diagnosis cholecystolithiasis. In-depth analyses of 294 patients showed a referral rate of 79.2% (n=233); 62.9% (n=185) underwent cholecystectomy. After referral, 55.4% (129/233) returned to the GP for persistent abdominal symptoms. Patients returning after referral were more often treated for another abdominal-related diagnosis before cholecystolithiasis was recorded (51.9% vs. 28.8%, $P < 0.001$).

CONCLUSIONS The majority of patients in general practice with gallstones are referred and undergo cholecystectomy. Patients with concomitant abdominal-related diagnoses are likely to return to their physician. GPs should inform patients about these outcomes to improve the shared decision-making process before gallbladder surgery.

INTRODUCTION

Cholecystolithiasis constitutes a significant and growing health problem in an increasingly obese population. Annually, Dutch hospital registrations record over 30.000 patients diagnosed with cholecystolithiasis, of whom 75% undergo surgery. In the United States, over 300,000 cholecystectomies are performed per year. (1) There is clear consensus that cholecystectomy is indicated for patients who develop biliary complications such as cholecystitis and biliary pancreatitis. The indication is less clear for patients who present with cholecystolithiasis and abdominal pain. (2-4)

A recent clinical trial (SECURE-trial) addressed the lack of consensus on the indication for surgery for uncomplicated cholecystolithiasis. This trial randomized 1,067 patients to usual care or a restrictive policy in which surgery was only performed after strict diagnostic criteria were met. (5)After one year follow-up, 40% of the patients suffered from persistent abdominal pain regardless the study arm. A possible explanation is that many patients with cholecystolithiasis and abdominal pain have features of functional gastro-intestinal disorders, and this category in particular had a higher risk of persistent postoperative pain. (6) The mediocre outcome of cholecystectomy supports the need for better patient selection for surgery and to better inform patients in order to manage expectations.

The information on the outcome of treatment for cholecystolithiasis patients is to a large extent derived from studies with a secondary care perspective. Little is known on the diagnostic care pathway of patients with cholecystolithiasis within primary care. For the present study, we collected clinical data of patients diagnosed with cholecystolithiasis in primary care and assessed their healthcare utilization, presence of other abdominal-related diagnoses, and outcome of referral to secondary care. The purpose was to evaluate the outcomes of treatment for referred and non-referred patients, and secondly to determine differences in patients with and without cholecystectomy.

METHODS

Setting

We analysed registry data from 17 general practices affiliated with the Radboud University Medical Centre Practice Based Research Network in Nijmegen, the Netherlands. Subsequently, for in-depth analysis, we studied data from the medical records in a subset of seven affiliated practices. These practices were elected for feasibility purposes. Registry data extraction was performed by the Radboudumc Technology Centre Health Data (department for Primary and Community care), which provides support for extraction and secure storage of routine data. The Radboudumc Technology Centre adheres to

the regulations of Dutch and European laws and gained consent from the Radboudumc Medical Ethics Review Committee (number 2020-6871) for this study. Informed consent from individual patients for a retrospective study with anonymized patient data is not mandatory under Dutch Law. We used the STROBE cohort checklist when writing our report. (7)

Study population and patient selection

Patients were eligible for inclusion if aged eighteen years and older and diagnosed with cholecystolithiasis between January 2012 and December 2016. Diagnosis was defined by the International Classification of Primary Care (ICPC), which allows categorization of data in an episode of care structure. Patients were only eligible for inclusion if they were registered with their GP at least three years prior and three years after the diagnosis cholecystolithiasis. This selection resulted in a complete time interval of six years to assess the diagnostic pathway, referral pattern and follow-up.

Variables and outcomes

For the primary outcome, we studied healthcare utilization in the registry data. Healthcare utilizations was defined as laboratory diagnostics and prescribed medication for six years, three years leading up to the diagnosis of cholecystolithiasis plus three years of follow-up. Additionally, we assessed the number of recorded abdominal-related diagnoses (e.g. abdominal pain, stomach-ache, acid-related disease, constipation, irritable bowel syndrome) within the same timeframe, according to the registered ICPC codes (for details on collected registry data see supplementary data Table S1).

For the secondary outcomes, the following data was extracted from the Electronic Medical Records (EMRs) of individual patients: age, sex, BMI, abdominal symptoms, presence of biliary colic, cholecystolithiasis on abdominal imaging (ultrasound, computerized tomography or magnetic resonance cholangiopancreatography), department specific referral, time interval between diagnosis and referral, acute biliary presentations in the emergency department, and cholecystectomy. In referred patients, the number of repeat visits due to persistent abdominal symptoms and newly recorded abdominal pain-related diagnoses were assessed (for details on collected individual patient data see supplementary data Table S2). Complaints recorded within 6 weeks of surgery were considered to be surgery-related and were not scored.

Definitions for primary care treatment, referral and patients returning after referral

Initial treatment was defined as treatment by the GP (e.g. wait-and-see policy with lifestyle advice or prescription of medication), or referral to secondary care with cor-

responding treatment. Referred patients were defined as patients who visited the hospital outpatient clinic of the department of surgery, gastroenterology, or presented to the emergency department (ED) which was documented in the patient medical file. Patients treated in ED were regarded as patients with an acute biliary presentation (due to severe biliary colic, cholecystitis, or biliary pancreatitis). Patients who were referred to another medical specialist or were only treated by the GP were considered as non-referred patients. Patients who returned to their GP for abdominal-related complaints after referral were considered as returning patients.

Comparison of patients with different treatment trajectories

Different patient groups were compared to assess characteristics or symptoms associated with referral and cholecystectomy. Patients with and without referral and patients with and without cholecystectomy were compared. Secondly, differences in treatment outcomes were determined between these groups regarding the number of patients returning for persistent abdominal symptoms.

Patient and Public Involvement

No patient involved.

Statistical analyses

Descriptive statistics were used to summarize baseline characteristics. Continuous variables were presented as mean with standard deviation in case of normally distributed data and median with interquartile range (IQR) for skewed data. Categorical variables were compared using the chi-square test, and continuous data was compared using unpaired t-tests for normally distributed data or Mann-Whitney U tests for skewed data. To determine whether the individual patients were comparable in terms of age, gender and BMI to the registry cohort, these variables were tested for a significant difference. A *P*-value of less than 0.05 indicated statistical significance. All statistical analyses were performed in IBM SPSS Statistics Software, version 25.

RESULTS

Patients

After exclusion of six patients under 18 years-of-age, a total of 633 patients from 17 practices were included in the registry analysis. For the in-depth analysis, seven general practices from the network also provided data from medical files of 294 patients.

Registry data: the typical patient with cholecystolithiasis treated in primary care

Analysis of the registry data resulted in an infographic illustrating the typical patient with cholecystolithiasis treated in primary care (Figure 1). The mean age at the time of the diagnosis of cholecystolithiasis was 54.7 years. Male/female ratio was 1:1.6 and the mean BMI was 29.8 kg/m^2. Liver function tests were performed in 511 out of 633 patients (80.7%). Medication was prescribed in 95% of patients. Most commonly prescribed medication were NSAIDs (83.5%), medication for gastric disease (79.5%), and other analgesics (61.3%).

During 6 years, concomitant abdominal-related diagnoses were recorded in 56.9% of patients. Most frequent recorded ICPC-codes were abdominal pain (30.5%), stomach-ache (13.7%), constipation (10.6%), and acid-related disease (10.0%).

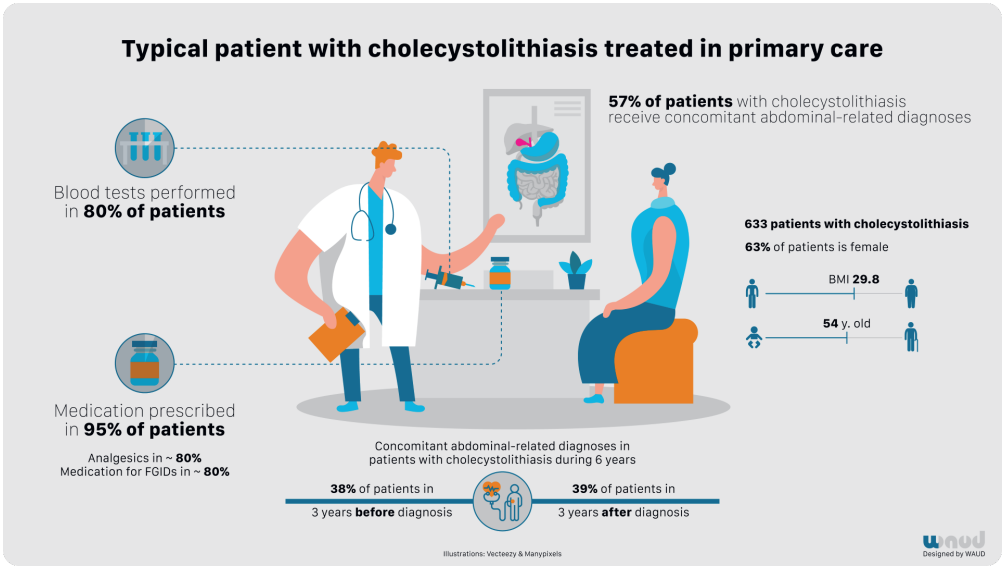

Figure 1 Typical patient with cholecystolithiasis treated in primary care. Registry data from 633 patients. BMI, body mass index.

Patients with cholecystolithiasis: characteristics, referral patterns, operation rates and patients returning after referral

The medical files of 294 patients with cholecystolithiasis showed similar characteristics to the registry cohort in terms of age, sex and BMI (53.7 vs. 54.7 years, $P = 0.36$; 63.6% vs. 63% female, $P = 0.67$; and 29.5 kg/m^2 vs 29.8 kg/m^2, $P = 0.91$, respectively). GPs documented the presence of a biliary colic in 57.5% of patients (169/294). Cholecystolithia-

sis was confirmed by imaging in 227 patients (77.5%). Two hundred thirty-three patients (79.3%) were referred and 62.9% (n=185) underwent cholecystectomy. Patients were primarily referred to the surgery, gastroenterology or emergency department, in 42.5%, 10.3% and 47.2%, respectively. The median time interval between diagnosis and referral was 9 days (IQR 43). Figure 2 illustrates the differences in referral rate, referral location and the median time interval in weeks between the diagnosis and referral per primary care facility. No significant differences were observed in terms of referral rate and time interval to referral between the facilities.

After initial treatment, GPs recorded persistent abdominal symptoms in 52.4% of patients (n=154). Pain (38.4%) was the most commonly recorded diagnosis, followed by diarrhoea (6.8%).

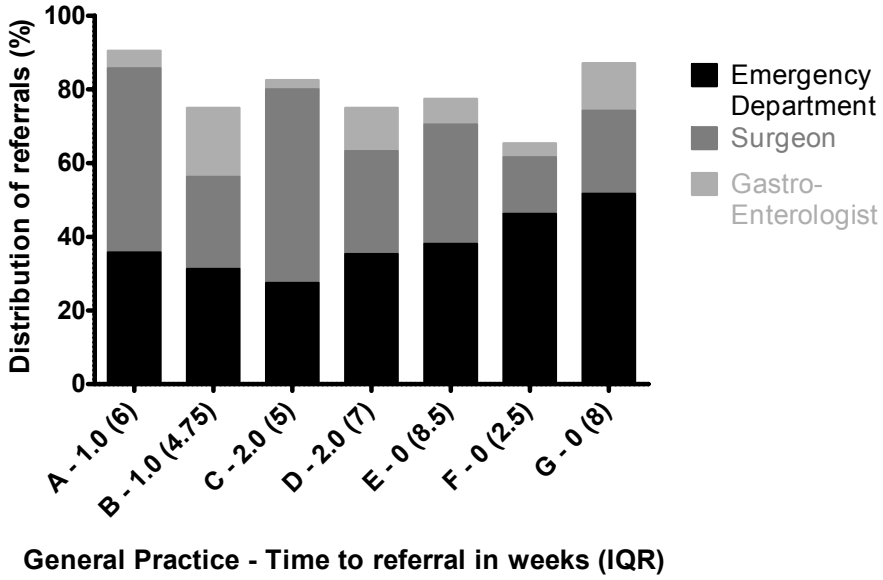

Figure 2 Difference in referral rate, location and time interval between diagnosis and referral among seven primary care practices (A–G). No significant difference was observed in the referral rate (p=0.19) or time interval (p=0.60) between diagnosis and referral among seven primary care practices.

Comparison of patients with and without referral

Patients with referral did not differ from patients without referral in terms of age, sex, BMI, frequency of blood tests, and prescribed medication (Table 1). GPs were more likely to refer patients to the hospital if a biliary colic was recorded (61.8% vs. 41.0%, $P = 0.003$). Moreover, during 6 years, referred patients more often visited their GP for abdominal symptoms (median 9 (IQR 8) vs. 6 (IQR 6), $P < .001$).

During follow-up after the diagnosis cholecystolithiasis, persistent symptoms were more often recorded in referred patients compared to patients without a referral (55.4% vs 41%, $P = 0.045$). Referred patients more often received an additional abdominal-related diagnosis after the diagnosis of cholecystolithiasis compared to non-referred patients (48.9% vs. 34.4%, $P < .001$). During follow-up, 24% (56/233) of previously referred patients were referred to secondary care for a second time due to persistent abdominal symptoms.

Acute biliary presentations

Hundred-ten patients (47.2%) were referred to the ED with an acute biliary presentation. No significant difference was observed between patients presented to ED versus patients referred to other departments in terms of age, sex and BMI. After presentation in ED, with or without cholecystectomy, these patients recorded similar persistent symptoms and frequency of repeat GP visits compared to patients without a presentation in ED.

Comparison of patients with and without cholecystectomy

Cholecystectomized patients were younger (53.1 vs. 57.7 years, $P = 0.045$), their initial referral was more often to the department of surgery (49.2% vs. 16.7%, $P < .001$) and less to the department of gastroenterology (7.6% vs. 20.8%, $P < .001$) or the emergency department (43.2% vs. 62.5%, $P < .001$). Less patients who underwent cholecystectomy reported pain during follow-up (36.2% vs. 60.4%, $P = 0.002$) (Table 1).

Outcome after referral

After referral, 55.4% of patients consulted their GP for persistent abdominal symptoms. Patients who return to their GP for persistent abdominal symptoms after referral were more often diagnosed with concomitant abdominal-related diagnoses prior to the diagnosis of cholecystolithiasis (51.9% vs. 28.8%, $P < .001$). Returning patients also visited their GP more often before the diagnosis of cholecystolithiasis (3 (IQR 3) vs. 2 (IQR 2), $P < .001$) (Table 2). A biliary colic was less often reported in returning patients (55.8% vs. 69.2%, $P = 0.04$).

Table 1. Characteristics and outcomes of patients with and without referral and with and without cholecystectomy.

	All patients (N = 294)	Referral (N = 233)	No referral (N = 61)	Referral	
				Cholecystectomy (N = 185)	No Cholecystectomy (N = 48)
Age, mean (SD)	53.7 (14.2)	54.1 (14.0)	52.4 (15.1)	53.1 (14.2)	57.7 (12.9)[#]
Sex, female (%)	187 (63.6)	147 (63.1)	40 (65.6)	122 (65.9)	25 (52.1)
BMI in kg/m², mean (SD)[a]	29.5 (5.7)	29.7 (5.7)	28.5 (5.8)	30.0 (6.5)	28.9 (4.7)
Concomitant abdominal-related diagnosis, n (%)	182 (61.9)	148 (63.5)	34 (55.7)	117 (63.2)	31 (63.5)
Before diagnosis cholecystolithiasis	116 (39.5)	93 (39.9)	23 (37.7)	74 (40.0)	19 (39.6)
After diagnosis cholecystolithiasis	135 (45.9)	114 (48.9)	21 (34.4)*	89 (48.1)	25 (52.1)
Number of consultations related to cholecystolithiasis or abdominal-related diagnoses, median (IQR)	8 (9)	9 (8)	6 (6)*	9 (8)	11.5 (11.75)
Before diagnosis of cholecystolithiasis	3 (3)	3 (3)	2 (2)*	3 (3)	3 (4)
After diagnosis cholecystolithiasis[b]	6 (6)	6 (6)	4 (5)*	6 (6)	6.5 (9)
Biliary colic, n (%)	169 (57.5)	144 (61.8)	25 (41.0)*	119 (64.3)	25 (52.1)
Referral to secondary care, n (%)	233 (79.3)	233 (100)	N/A	185 (100)	48 (100)
Dept. of Surgery		99 (42.5)	N/A	91 (49.2)	8 (16.7)[#]
Dept. of Gastroenterology		24 (10.3)	N/A	14 (7.6)	10 (20.8)[#]
Emergency Department		110 (47.2)	N/A	80 (43.2)	30 (62.5)[#]
Time interval between diagnosis and referral in days, median (IQR)	9 (43)	9 (43)	N/A	9 (42)	8 (72.25)

	All patients (N = 294)	Referral (N = 233)	No referral (N = 61)	Referral	
				Cholecystectomy (N = 185)	No Cholecystectomy (N = 48)
GP consultation for persistent abdominal symptoms after initial treatment, n (%)	154 (52.4)	129 (55.4)	25 (41.0)*	97 (52.4)	32 (66.7)
Type of symptoms					
Pain	113 (38.4)	96 (41.2)	17 (27.9)	67 (36.2)	29 (60.4)[#]
Heartburn	12 (4.1)	6 (2.6)	6 (9.8)*	6 (3.2)	0 (0)
Diarrhoea	20 (6.8)	19 (8.2)	1 (1.6)	16 (8.6)	3 (6.3)
Other	9 (3.1)	8 (3.4)	1 (1.6)	8 (4.3)	0 (0)
New referral to secondary care for persistent symptoms in 3 years after diagnosis of cholecystolithiasis, n (%)	56 (19.0)	56 (24.0)	N/A	41 (22.2)	15 (31.3)
Dept. of Surgery	12 (4.1)	12 (5.2)	N/A	9 (4.9)	3 (6.3)
Dept. of Gastroenterology	30 (10.2)	30 (12.9)	N/A	22 (11.9)	8 (16.7)
Dept. of Internal Medicine	7 (2.4)	7 (3.0)	N/A	5 (2.7)	2 (4.2)
Emergency Department	7 (2.4)	7 (3.0)	N/A	5 (2.7)	2 (4.2)

[a] *Based on 137/294 patients*

[b] *Complaints recorded within 6 weeks of surgery were considered to be surgery-related and were not scored.*

** A significant difference (P < 0.05) was found between referred and not referred patients*

[#] *A significant difference (P < 0.05) was found between patients who did or did not receive a cholecystectomy*

Table 2. Comparison of patients who did or did not return to their GP for persistent abdominal-related diagnoses after referral.

	Total (n=233)	Return to GP (n= 129)	No return to GP (n= 104)	P-value
Sex, female (%)	147 (63.1)	84 (65.1)	63 (60.6)	0.475
Age, mean (SD)	58.3 (13.8)	57.9 (13.8)	58.9 (14.1)	0.207
BMI, mean (SD)	29.8 (6.1)	30.2 (6.4)	29.2 (5.7)	0.387
An abdominal-related diagnosis recorded before cholecystolithiasis, n (%)	97 (41.6)	67 (51.9)	30 (28.8)	< .001
Number of consultations for abdominal-related diagnoses, median (IQR)	9 (7.75)	12 (9)	6 (4)	< .001
Before diagnosis of cholecystolithiasis	3 (3)	3 (3)	2 (2)	< .001
After diagnosis of cholecystolithiasis	6 (6)	8 (6)	4 (3)	< .001
Biliary colic, n (%)	144 (61.8)	72 (55.8)	72 (69.2)	0.036
Cholecystectomy, yes (%)	185 (79.4)	97 (75.2)	88 (84.6)	0.077

DISCUSSION

Summary

During 6 years of follow-up, liver function tests were performed in 81% of patients and medication was prescribed in 95% of patients. More than half of the patients referred for the treatment of cholecystolithiasis return to their GP for persistent abdominal symptoms irrespective of cholecystectomy. Patients with previous abdominal-related diagnoses are more likely to return after referral compared to patients without other initial diagnoses. Pre-existent abdominal-related symptoms are a major cause of persistent symptoms after cholecystectomy, and GPs should be aware about these suboptimal outcomes of referral to secondary care.

We found that liver function tests were performed in 81% of patients, while international guidelines do not advocate the use of laboratory tests in patients with uncomplicated cholecystolithiasis because they do not contribute to the diagnosis. (8) We also found that medication was prescribed in 95% of patients and NSAIDs were the most commonly prescribed drug. This is good practice, as a typical biliary colic should respond to simple analgesics. (8)

Persistent abdominal symptoms after cholecystectomy are a clinical dilemma and are accompanied by a significant burden for patient and healthcare system. (9) Causes for persisting pain relate to surgery, residual gallstones or undiagnosed alternative functional gastrointestinal disorders. (5, 10-12) The outcome of the present study in a primary care setting is in line with existing surgical literature reporting persistent postoperative pain in 40% of patients. Analysis of the SECURE-trial, a recent randomized-controlled trial designed to compare the conventional indication for cholecystectomy with a more restrictive and criteria-based strategy in patients with abdominal pain and ultrasound-proven gallstones, showed that the Rome III criteria (severe steady pain, lasting 30 minutes, located in the epigastrium and/or right upper quadrant) have limited validity in the selection of patients for cholecystectomy as these criteria are poorly associated with a postoperative pain-free state. (5) Selection of patients with uncomplicated cholecystolithiasis for referral for surgery is just as challenging. Previous studies have shown that a proportion of patients with uncomplicated cholecystolithiasis who are initially treated conservatively, may never require surgery. (9) There is an ongoing clinical trial in the UK that aims to randomize 430 patients to evaluate conservative medical management and cholecystectomy in terms of quality of life and cost-effectiveness. (13) The background for this trial are two Norwegian studies which suggest that conservative management may be a safe alternative to surgery in selected patients. About 55% of the 201 patients randomized to conservative management in these trials did not require surgery over a 14-year period. (14, 15) Another prospective cohort study by Berger et al. in primary care patients with suspected cholecystolithiasis showed that neither biliary pain nor any other gastrointestinal complaint was related to cholecystolithiasis consistently. The authors concluded that before the diagnosis symptomatic cholecystolithiasis is made, other common gastrointestinal pathology (e.g. reflux esophagitis and irritable bowel syndrome, should be excluded. (16) In our study, 40% of patients consulted their GP with symptoms resulting in another abdominal related diagnosis before the diagnosis cholecystolithiasis was set. Interestingly, this specific group of patients with a previous abdominal related diagnosis returned more often with persistent symptoms after referral. To aid clinicians to better select patients for cholecystectomy, we recently reported on an online decision tool. The variables included in this tool illustrate that patient characteristics, pain scores, surgical history and signs of functional gastrointestinal disorders are more the relevant factors to predict clinically relevant pain reduction after surgery. (17)

Cholecystectomy is indicated for complicated gallstone disease (e.g. Cholecystitis, biliary pancreatitis), while consensus among surgeons and gastroenterologists for the selection for cholecystectomy in uncomplicated gallstone disease is absent. (18) Underlying gastrointestinal disorders such as dyspepsia, heartburn, regurgitation or constipation hamper the outcome of cholecystectomy. Therefore, we advise GPs to address

these specific disorders and rule them out as a potential cause of abdominal pain. Although we are aware that functional disorders as obstipation, dyspepsia, or heartburn are sometimes difficult to differentiate from biliary pain, the results of this study may be of help in the process of informing the patient and shared decision-making about referral and surgery. This advice is endorsed by the results of the present study and the results of a recent study in secondary care in which the role of abdominal-related disorders was evaluated in patients with cholecystolithiasis. (6) We showed indecisive outcomes after surgery in 400 patients with abdominal pain and gallstones, especially if irritable bowel syndrome or dyspepsia were present. Noticeably, our study found that over half of patients with cholecystolithiasis also received concomitant abdominal-related diagnoses, while this percentage in the general population is around 40%. (19) A wait-and-see policy with an interval of a few weeks is preferred, as this policy generally discriminates more adequately between biliary and non-biliary pain relative to additional diagnostic tests or an invasive gastrointestinal endoscopy.

The strength of the present multi-practice study is the three-year time interval before and after the diagnosis cholecystolithiasis. This interval optimized the assessment of the diagnostic pathway, medication prescription and referral pattern in this patient group. The analysis of EMRs of 294 patients provided real-life information on healthcare utilization and type of received treatment in secondary care facilities. We acknowledge this study comes with some limitations. Firstly, data was collected retrospectively, which may lead to information bias. Secondly, registry data laboratory diagnostics and prescribed medication may not only relate to the diagnosis cholecystolithiasis and detailed hospital data were not available. Finally, even though the EMRs ensure complete information, differentiation between different diagnoses may not always be accurate. GPs may record the diagnosis cholecystolithiasis without the presence of typical complaints. The analysis of the subset showed this may have applied to the registry data, as a biliary colic was only reported in 57% of patients. This illustrates the complexity of diagnosing patients with abdominal-related symptoms in primary care.

Implications for practice

This study found that patients with cholecystolithiasis are often referred to a hospital while half of these patients return with persistent abdominal symptoms. The high prevalence of abdominal-related diagnoses before the diagnosis of cholecystolithiasis in patients with repeat visits stresses the fact that GPs should be precarious when referring patients with non-typical complaints. Shared decision-making before referral is necessary, especially in patients with another initial abdominal-related diagnosis. It is pivotal to manage patients' expectations on the outcomes of cholecystectomy early in the referral chain, making a clear distinction between the beneficial effect on biliary colic

and questionable effect on non-biliary abdominal pain. This study adds to the growing awareness that there is no consensus within our medical community on the indication for cholecystectomy in patients with uncomplicated cholecystolithiasis and abdominal pain. GPs, gastroenterologists and surgeons are cordially invited to discuss the present findings and to collaborate on optimizing criteria for diagnostics, referral and treatment of this large group of patients.

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CHAPTER

3

Patients with clinically suspected gallstone disease: a more selective ultrasound may improve treatment related outcomes

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Journal of Clinical Medicine 2023

ABSTRACT

OBJECTIVE This study aimed to quantify the confirmation of gallstones on ultrasound (US) in patients with suspicion of gallstone disease. To aid General practioners (GP) in diagnostic work-up, a model to predict gallstones was developed.

METHODS A prospective cohort study was conducted in two Dutch general hospitals. Patients (≥18 years) were eligible for inclusion when referred by GP for US with suspicion of gallstones. The primary outcome was the confirmation of gallstones on US. A multivariable regression model was developed to predict the presence of gallstones.

RESULTS In total 177 patients were referred with a clinical suspicion of gallstones. Gallstones were found in 64 of 177 patients (36.2%). Patients with gallstones reported higher pain scores (VAS 8.0 vs 6.0, P<.001), less frequent pain (21.9% vs. 54.9%,P< .001) and more often met criteria for biliary colic (62.5% vs 44.2%, P=.023). Predictors for presence of gallstones were: higher pain score, frequency of pain less than weekly, biliary colic, and absence of heartburn. The model showed good discrimination between patients with and without gallstones (C-statistic 0.73, range: 0.68-0.76).

CONCLUSIONS Clinical diagnosis of symptomatic gallstone disease is challenging. The model developed in this study may aid in the selection of patients for referral and improve treatment related outcomes.

INTRODUCTION

The occurrence of gallstone disease is a significant and rising health issue in Western society. (1) International guidelines advise laparoscopic cholecystectomy as treatment for symptomatic and complicated cholecystolithiasis. (2-4) Laparoscopic cholecystectomy is the most commonly performed gastrointestinal surgical procedure, resulting in 80.000 surgeries in the United Kingdom and 24.000 in the Netherlands annually. (5) In the Netherlands, the surgery rate of patients with symptomatic gallstone disease is approximately 70%. (6) Symptomatic cholecystolithiasis is an ill-defined condition ranging from epigastric pain to steady, non-paroxysmal pain in the presence of gallstones on transabdominal Ultrasound (US). (7) Due to underlying functional gastrointestinal diseases (FGID) and lack of consensus on patient selection, up to 40 percent of patients report persisting upper abdominal pain (UAP) after cholecystectomy. (7-9)

The SECURE trial has shown that fulfilment of the ROME III criteria for biliary colic (severe steady pain, lasting 30 minutes or more, located in the epigastrium and/or right upper quadrant), is a poor predictor of pain relief after cholecystectomy. (10) This recently performed multicentre RCT showed that a restrictive strategy, based on the selection for surgery on the ROME III criteria results in 8% fewer cholecystectomies, but more patients with persistent pain. (8) The outcome of the trial emphasized the need for better criteria to select patients that will benefit from surgery. A recent analysis of Dutch primary care registry data from 633 patients showed that more than half of the patients referred for treatment of gallstones return to their General Practitioner for persistent abdominal symptoms irrespective of cholecystectomy. (11) The high number of returning patients illustrates to the importance of better selecting patients for surgery early in their trajectory. Patients' expectations of diagnostics and treatment influence decision-making and play an essential role in patient reported outcome. (12, 13)

To aid in the diagnostic workup and decision-making in patients with UAP and clinical suspected gallstone disease, the present study aims to quantify the outcome of US. Second, a multivariable regression model was developed to predict the occurrence of gallstones. Patient selection based on easily available patient characteristics and symptoms would be of considerable value for clinical decision-making and patient expectations.

MATERIALS AND METHODS

Study Design

This prospective cohort study was conducted in patients with a clinical suspicion of gallstone disease who were referred for a US under direct responsibility of the GP at the

Department of Radiology of two general hospitals in The Netherlands (Jeroen Bosch Hospital, 's-Hertogenbosch and Northwest clinics, Alkmaar). Patients were approached for participation between May 2018 and July 2020. Patients ≥18 years of age who were clinically suspected of gallstone disease by their GP were eligible for inclusion. Patients were not eligible for inclusion if: the clinical suspicion of gallstone disease was not stated in the referral letter, they had a history of cholecystectomy or were referred for US for other reason. Additionally, exclusion criteria were: history of complicated cholecystolithiasis (i.e., choledocholithiasis, acute cholecystitis, biliary pancreatitis or cholangitis), previous malignancy, pregnancy, active mental disorder or incompetence that influences reliability of questionnaire response, or insufficient knowledge of the Dutch language.

This study was approved by the medical ethics commission (METC: 2017-3306) and performed in accordance with the ethical standards of the updated Helsinki Declaration of 2013. We followed Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines. (14)

Recruitment and Selection of Study Subjects

Patients were contacted by telephone before the appointment for a US to assess in- and exclusion criteria and to discuss consent for participation. All eligible patients who gave informed consent received a paper or digital baseline questionnaire. Follow-up questionnaires were sent after six months. A reminder at baseline and follow-up was sent to participants who did not respond.

Measurements

the questionnaire consisted of the Izbicki Pain Score (IPS) and questions on abdominal symptoms. The IPS consists of four questions regarding frequency of pain, intensity of pain based on a Visual Analog Scale (VAS-score, 0 = no pain and 10 = worst imaginable pain), use of pain medication and disease-related inability to work. (15) The IPS score is expressed as continuous pain scale (IPS-score, 0 = no pain and 100 = worst imaginable pain).

After 6 months follow-up clinical data were obtained from the medical records on health care consumption in secondary care level. Clinical data and health care consumption in primary care were not collected.

Outcomes

The primary outcome was the occurrence of gallstones or sludge on US in patients with a clinical suspicion of gallstone disease according to the GP. Clinical suspicion of gallstones was scored when a GP referred a patient with the question of possible gallstone

disease, symptomatology was generally not, or very briefly, reported on the referral. US-proven gallstones included positive findings of gallstones or sludge in the gallbladder. US report was retrieved from patients' medical record from the hospital. Secondary endpoints were comparisons between patients with and without gallstones treatment related outcomes at six months.

A prediction model was developed to assess predictive factors for the presence of gallstones and/or sludge on US in patients with a clinical suspicion of gallstone disease as stated by GP. In order to ensure sufficient power, a minimum of 10 outcome events per selected predictor variable was applied as a rule of thumb (EPV). (16) Seven variables collected at baseline were entered in the model: biliary colic according to ROME III-criteria, pain characteristics (pain radiation to the back, use of simple anaesthetics, frequency of pain, VAS pain score), heartburn and nausea. VAS pain score was entered as squared function because of non-linearity. Baseline predictor information was retrieved from the survey at baseline. Discrimination was quantified by the Area under the Curve (AUC).

Number of cholecystectomies and pain-free patients at six months of follow-up was assessed by the survey. Definition of Pain or Pain-free is in line with previous SECURE-trial and SUCCES-trial: IPS score ≤10 and a VAS pain score ≤4. (8, 15, 17)

Statistical Analysis

Missing data at baseline were imputed using a multiple imputation strategy (30 sets) and predictive mean matching for continuous variables. (18) Patients with missing data in follow-up questionnaires after six months were excluded from the follow-up analyses, instead of using multiple imputation, because outcomes at baseline were defined as primary outcome. Responders and non-responders were compared on baseline characteristics (e.g. sex, age and presence of gallstones), along with patients who did and did not withdrew their consent.

Baseline characteristics (age, BMI) and information from the survey (pain scores and abdominal symptoms) were presented as mean with standard deviation when normally distributed and median with range or inter quartile range (IQR) when data were not normally distributed. Dichotomous data were summarized by frequencies and proportions (pain characteristics, fulfilment of the ROME criteria and abdominal symptoms). Differences between patients with and without gallstones were analysed using chi-squared test, Fisher's exact test, independent t-test and Mann-Whitney-U test, depending on the type of data. Normality of data distributions was based on the Shapiro-Wilk test. P-values of less than 0.05 indicated statistical significance.

A multivariable logistic regression analyses with backward selection was performed to

assess predictors at baseline for detection of gallstones in patients. US confirmed gallstones yes/no served as outcome in this model. The model's performance was assessed by discrimination ability to differentiate between patients with and without gallstones. Based on the recent findings regarding to the ROME III criteria in the SECURE trial, the discrimination ability of model with solely the ROME III criteria was assessed.[7] The threshold for variable-selection was 0.15. Receiver operating characteristic curve (ROC) with area under the curve (AUC) analysis was used to evaluate the performance of the model to differentiate between patients with and without gallstones. Data analysis was performed using IBM SPSS, version 27 (SPSS Inc.).

RESULTS

Patient Characteristics

In total, 329 patients were assessed for eligibility. Forty-five patients (13.7%) were not eligible for inclusion because of: no stated clinical suspicion of gallstone disease in referral letter (N=15), patients with history of cholecystectomy (N=5), or other reason for US (N=25). Of 284 included patients, eighty-two patients (28.9%) declined to participate, and 25 patients (8.8%) withdrew informed consent. No significant differences were found in basic patient characteristics (i.e. sex and age) regarding included patients and patients who withdrew informed consent. This resulted in a final study sample of 177 patients (Figure 1). Characteristics of patients included for analyses are shown in Table 1.

Confirmation of Gallstones on Ultrasound in Patients with Clinical Suspicion of Gallstone Disease

In total, 177 patients were specifically referred for US because of a clinical suspicion of gallstones. In 64 of these 177 patients (36.2%), the presence of gallstones was confirmed by US. Sludge was found in 4.7%, a thickened gallbladder wall in 2.8% of patients with gallstones.

Comparison of Patients with and without Gallstones

In Table 1 baseline characteristics of patients with (n=64) and without (n=113) gallstones are compared. Patients with gallstones reported more severe pain (VAS-score: median 8.0 (IQR 5.5-9.0) vs. 6.0 (IQR 4.0-7.5), $P < .001$), which occurred less frequently (weekly pain: 21.9% vs. 54.9%, $P < .001$) and for which they used pain medication more often (56.3% vs. 33.6%, $P = 0.003$). Patients with gallstones met criteria for a biliary colic more often (62.5% vs. 44.2%, $P = 0.023$) compared to patients without gallstones on US.

Patients without gallstones reported more abdominal bloating compared to patients with gallstones (22.1% vs. 7.8, P = 0.026). Age, sex and BMI were comparable between the two groups.

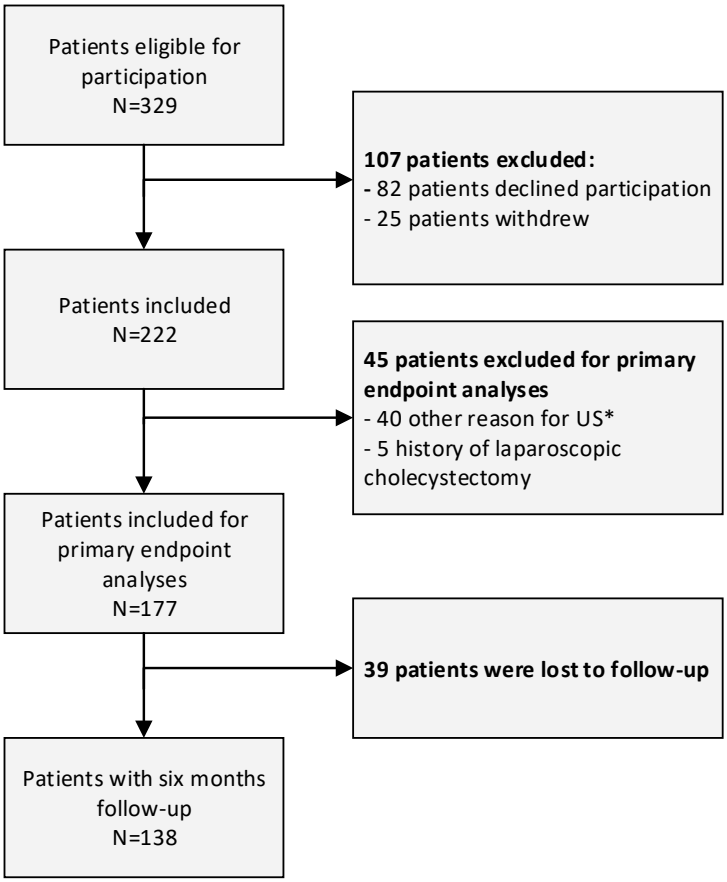

Figure 1. Flowchart of included patients with clinical suspicion of gallstone disease. Patients ≥18 years of age with clinical suspicion of gallstone disease were referred by their GP for a direct access US, were eligible for primary endpoint analyses.

Table 1. Baseline characteristics of patients included with and without gallstones on US. Clinical suspicion of gallstones was scored when GP referred patient for a direct access US with the question of possible gallstone disease or sludge.

	Total (N=177)	Gallstones (N=64)	Absence of gallstones (N=113)	P
Baseline characteristics				
Age, mean (SD)	54.8 (15.4)	56.1 (14.8)	53.8 (16.0)	0.384
Sex, Female n (%)	119 (67.2)	46 (71.9)	73 (64.6)	0.322
BMI, mean (SD)	26.8 (4.7)	27.2 (4.3)	26.5 (4.9)	0.354
Consumes alcohol, n (%)	126 (71.2)	44 (68.8)	82 (72.6)	0.590
Current smoker, n (%)[ˆ]	28 (15.8)	4 (6.3)	24 (21.2)	0.009
Abdominal surgery in history, n (%)	51 (28.8)	18 (28.1)	33 (29.2)	0.879
Abdominal pain				
Izbicki Pain Score, median (IQR)	32.5 (26.9-40.0)	31.2 (26.8-37.6)	33.7 (26.8-42.0)	0.185
VAS pain score, median (IQR)	7.0 (4.0-8.0)	8.0 (5.5-9.0)	6.0 (4.0-7.5)	*P*<.001
Biliary symptoms*				
Severe pain attacks, n (%)	128 (72.3)	50 (78.1)	78 (69.0)	0.194
Pain in right upper quadrant/ epigastric region, n (%)	148 (83.6)	55 (85.9)	93 (82.3)	0.530
Duration of pain longer than 15-30 min, n (%)*	137 (77.4)	56 (87.5)	81 (71.7)	0.020
Biliary colic, n (%)*	90 (50.8)	40 (62.5)	50 (44.2)	0.023
Pain radiating to the back, n (%)	96 (54.2)	36 (56.3)	60 (53.1)	0.686
Use of pain medication, n (%)	74 (41.8)	36 (56.3)	38 (33.6)	0.003
Urge to move, n (%)[β]	45 (25.4)	15 (23.4)	30 (26.5)	0.998
Weekly pain, n (%)[β]	76 (42.9)	14 (21.9)	62 (54.9)	*P*<.001
Functional symptoms[β]				
Difficult defecation, n (%)[#]	14 (7.9)	1 (1.6)	13 (11.5)	0.026
Diarrhoea, n (%)[β]	12 (6.8)	3 (4.7)	9 (8.0)	0.495
Heartburn, n (%)[β]	17 (9.6)	3 (4.7)	14 (12.4)	0.133
Abdominal bloating, n (%)[β]	30 (16.9)	5 (7.8)	25 (22.1)	0.026
Nausea/Vomitus, n (%)	15 (8.5)	6 (9.4)	9 (8.0)	0.604

*[ˆ] 1 missing; * 1 missing; [β] 19 Missings; [#] 18 missings; Abbreviations: BMI, body mass index (calculated as weight in kilograms, divided by height in meters squared): IQR, interquartile range; VAS, visual analog scale.*

Prediction Model

The prediction model for gallstones on US included the following variables: biliary colic in accordance with the ROME III criteria, absence of heartburn, frequency of pain, and VAS pain score. It showed good discriminative ability (AUC 0.73, range 0.68-0.76) (Figure 2). Regression coefficients and odds ratios of the model are shown in Table 2. The discriminative ability of the ROME III criteria for biliary colic alone was poor (AUC 0.59, range 0.57-0.61).

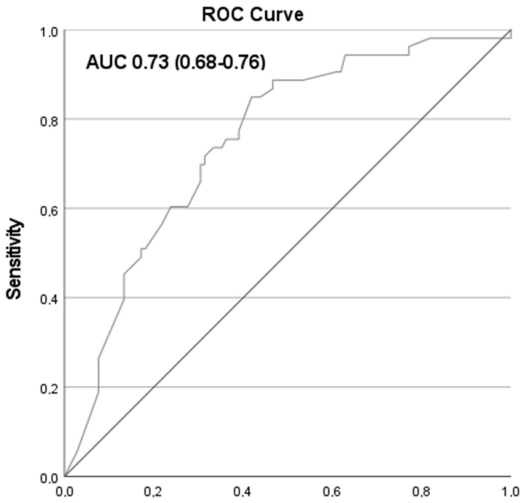

Figure 2. Calibration plot of the prediction model for presence of gallstones in patients with upper abdominal pain. Calibration plot of the prediction model for presence of gallstones on abdominal ultrasound in patients with clinical suspicion of gallstone disease. The green line is the ideal line. The blue line is the Area under the Curve (AUC).

Table 2. Predictors for presence of gallstones in patients with clinical suspicion of gallstone disease by GP. Multivariable logistic regression analyses with backward selection was performed to assess predictors at baseline for detection of gallstones in patients. US confirmed gallstones yes/no served as outcome. The threshold for variable selection was 0.15. Model development was based on 177 patients.

Predictors	**Odds ratio (95% CI)**
Intercept	
Presence of biliary colic according to ROME-criteria	
No	1 [Reference]
Yes	1.36 (0.63-2.92)
VAS pain score squared*	
No pain	1 [Reference]
Per step	1.05 (0.99-1.11)
Heartburn	
No	1 (Reference)
Yes	0.61 (0.12-3.08)
Frequency of pain is weekly	
No	1 [Reference]
Yes	0.35 (0.15-0.83)
AUC	0.73 (0.68-0.76)

VAS: visual analogue scale. AUC: Area Under the Curve.
** VAS pain score was entered as squared function because of non-linearity*

Outcomes at Six Months Follow-Up

Of all patients, 77.9% (138/177) responded to the follow-up questionnaire at 6 months. No significant differences were found between responders and non-responders in terms of age, sex, or the presence of gallstones. In 39 of 138 patients (28.3%), reported persisted abdominal pain. During follow-up, 49 of 64 (76.5%) patients with gallstones were referred to the surgical outpatient clinic, of whom 36 (73.5%) underwent laparoscopic cholecystectomy. At six months follow-up, patients without gallstones reported more persisted pain compared to patients with gallstones (37.2% vs. 13.5%, P = 0.003).

DISCUSSION

Main Findings

The diagnostic work-up in the large group of patients with clinical suspicion of gallstone disease is challenging. The present study illustrates that gallstones were not confirmed in 64% of patients of with a clinical suspicion of gallstones described by the GP. The outcome of this study resulted in a model to better select patients for US. The model is based on clinical pain characteristics, frequency of pain, and the absence of heartburn. The present findings are summarized in a decision tree, which may help during the option talk with patients who report UAP on the benefit of additional diagnostics (Figure 3).

Strengths and Limitations

This prospective multicentre study has strengths and limitations. Our findings provided new insights into the diagnostic pathway for patients with UAP and accentuated the complexity of correctly diagnosing symptomatic cholecystolithiasis. Secondly, validated questionnaires were used to assess abdominal pain and symptoms. A limitation was the relatively small sample size of the present study. (19) However, the sample size was sufficient for the number of variables we studied, but for a more extensive study with many more predictors a larger sample will be needed. (20-22) Nevertheless, the AUC is good and the range reasonable (AUC = 0.73, range 0.68-0.76). It is also considerably better in predicting the presence of gallstones than currently used ROME-criteria (AUC = 0.59, range 0.57-0.61).

Comparison with Existing Literature

This study echoes the results of Berger et al. published in 2004. Based on their research on 233 primary care patients, the authors stated that neither biliary pain nor any other gastrointestinal symptomatology was related to gallstones consistently. (23, 24) The authors concluded that before the diagnosis of symptomatic gallstones is made, other reasons of upper abdominal pain and symptoms (i.e. FGID) should be ruled out. Likewise, the present analysis revealed that the ROME III criteria alone are inadequate for predicting the presence of gallstones on US, as heartburn and the frequency of pain appeared to be important predictors. Berger and colleagues already called for additional data from a randomized controlled trial to clarify the indication for cholecystectomy. Almost twenty years later, outcomes of such studies are available. (23)

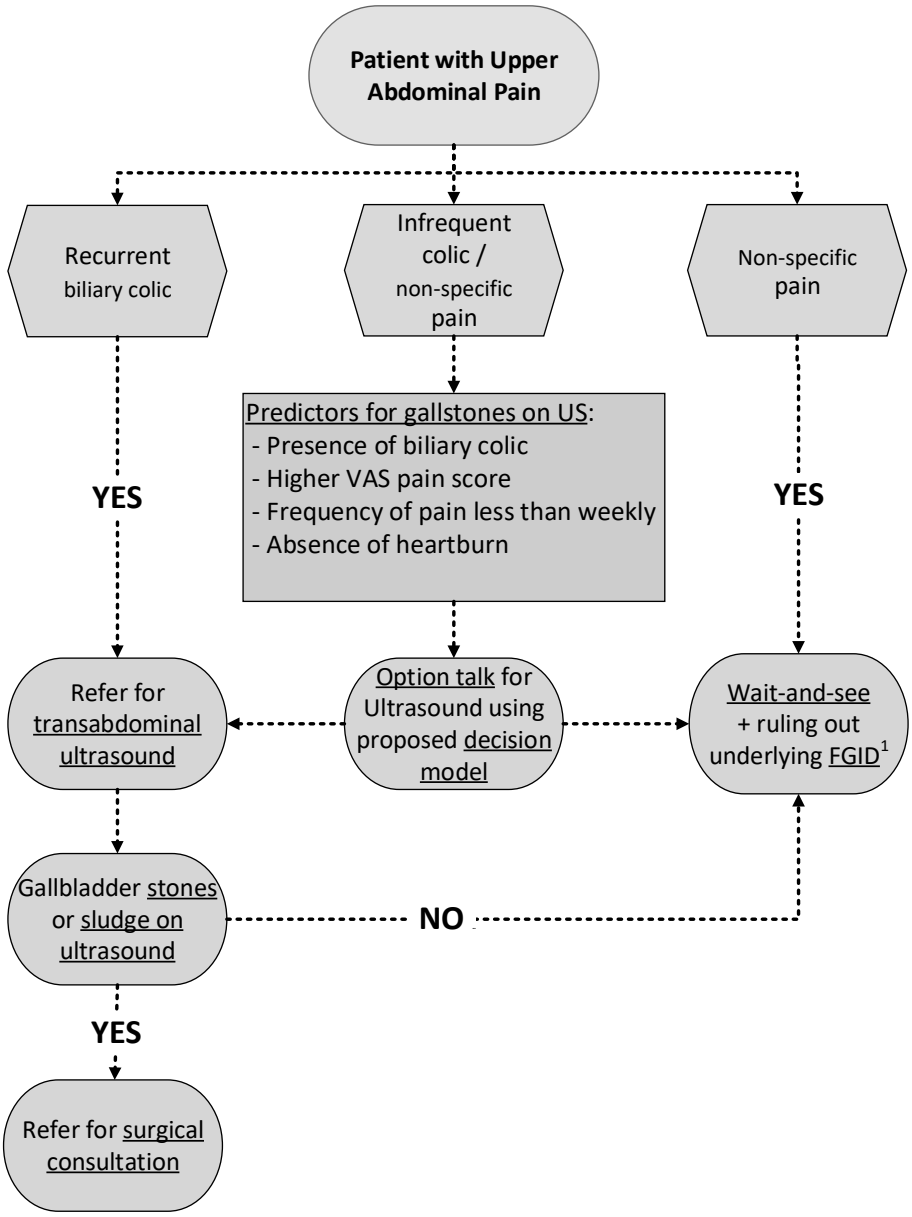

Figure 3. Decision tree for the diagnostic work-up of patients with upper abdominal pain in primary care. During consultations, different diagnostic and treatment options and possible outcomes are open for discussion. [1]FGID: functional gastrointestinal diseases (i.e., functional dyspepsia and/or irritable bowel syndrome).

Two studies illustrated the challenge to define symptomatic gallstone disease, and subsequently showed the negative impact of presence of FGID on the outcome of a cholecystectomy. In 2011 Thistle et al. presented the results of their prospective study in 1008 patients undergoing cholecystectomy for symptomatic gallstone disease. Fifty-nine percent of patients were pain-free after one year of follow up. Independent predictors of pain relief were frequency of pain less than once a month, the onset of pain less than 1 year before surgery and nocturnal pain. (25) Moreover, functional symptoms were negatively associated with pain relief. The Dutch PERFECT-trial found similar results in a multicentre cohort study of 401 gallstone patients. The baseline characteristics showed that one third of patients with gallstones also fulfil criteria for FGID. Patients with these concomitant conditions were 2.5 times less likely to become pain-free after surgery. (26)

The diagnostic work-up of patients with UAP generally consists of laboratory tests, abdominal US or an upper gastrointestinal endoscopy, and FGID, irritable bowel syndrome, gallstones and dyspepsia are the most common diagnosis. (11) Speets et al. reported a diagnostic yield for detection of gallstones on US of 8%. This study was conducted in an academic hospital with a diverse patient population. (13) Detection of gallstones on US is often coincidental, while the risk of missing the diagnosis cholecystolithiasis is relatively harmless. Less than 5% of symptomatic gallstone patients develop a biliary complication. (27) Likewise, our study shows a diagnostic yield of US (36.2%). Moreover, previous studies showed a mediocre therapeutic yield, while 40% of patients is not free of UAP after cholecystectomy. Considering these outcomes, 100 referrals for an ultrasound of patients with a suspicion of gallstone disease result in 14 patients being pain-free after treatment, and the prevention of 1-2 biliary complications. (8) Therefore, informing the patient on the various causes of UAP and the different options for clinical work-up including lifestyle measures is a corner stone for the treatment of patients with UAP. This form of stepped care is safe and will postpone referral for US and may prevent unnecessary surgery.

To reduce unnecessary surgery an online decision tool was recently developed to aid surgeons in selecting patients for cholecystectomy. Based on data from 1561 patients with symptomatic gallstone disease, this tool predicts the probability of pain reduction after cholecystectomy. The tool aids surgeons in deciding whether patients with uncomplicated gallstone disease will benefit from surgery. Variables included in the model illustrate that heartburn, pain scores, surgical history and patient characteristics are valuable in predicting clinically relevant pain reduction after cholecystectomy. (17)

Implications for Practice

The model based on this study may be helpful to move forward and facilitate an evidence-based option talk between GPs and patients with suspected gallstone disease. A

proposal for a patient trajectory, including option talks for patients with UAP, is shown in Figure 3. During consultations, different diagnostic and treatment options and possible outcomes are open for discussion. The model proposed in this study and the clinical decision tool help better select patients with symptomatic gallstone disease for cholecystectomy, and might optimise patients‘ expectations and reduce ineffective use of health care resources. (17) The latter may be accomplished by reducing the number of US performed in patients with UAP, but in whom a laparoscopic cholecystectomy will be a mediocre solution to reduce pain. Tailored expectations regarding the outcome of the treatment help patients not always to choose an operation.

Conclusions

In conclusion, this study shows that two thirds of patients referred for US because of a suspicion of gallstones, the diagnosis of symptomatic gallstone disease cannot be confirmed. The high suspicion of gallstones in patients with abdominal pain and symptoms underlines the complexity of correctly diagnosing gallstone disease in primary care. The present prediction model aids GPs in decision making, and we advise GPs to address uncertain outcomes of referral and rule out possible gastrointestinal disorders before the patient is referred for US on suspicion of gallstones.

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CHAPTER

4

The impact of surgical capacity shortages on disease-related morbidity in benign conditions: a comparative cohort study of gallstone and inguinal hernia care during the COVID-19 pandemic

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BMC Surgery 2026

ABSTRACT

BACKGROUND With increasing pressure on operating room capacity due to growing surgical demand and constraints in cost, workforce, and sustainability, real-world scenarios such as the COVID-19 pandemic offer valuable insights. This study assessed the pandemic's impact on surgical care for patients with gallstone disease or inguinal hernia, focusing on disease-related and surgical complications.

METHODS This multicenter historical cohort study included patients treated in 2019 and 2020 at three Dutch hospitals. Data were collected from hospital systems and patient records. The COVID period (March–December 2020) was compared to a reference period (March–December 2019). The primary outcome of this study was the rate of disease-related complications. Secondary outcomes included surgery rates, hospital presentations and admissions, time to surgery, surgical complications, length of hospital stay, and readmissions.

RESULTS In total, 1572 patients with gallstone disease and 1511 with inguinal hernia were included. During the COVID period, fewer cholecystectomies were performed (59.8% vs. 67.7%, p = 0.001), and complicated gallstone disease increased (28.5% vs. 21.6%, p = 0.002). No significant differences were found in the rate of inguinal hernia repairs (61.6% vs. 63.5%, p = 0.46) or hernia-related complications (5.4% vs. 3.7%, p = 0.139). Surgical complication rates were similar across both periods for both conditions.

CONCLUSIONS Limited surgical availability during the COVID-19 period was linked to reduced cholecystectomy rates and more complicated gallstone disease, without affecting inguinal hernia outcomes or surgical complication rates.

INTRODUCTION

The aging population, coupled with challenges related to high costs, limited human resources, and sustainability concerns, places strain on surgical care, necessitating prioritization within limited capacity. During the COVID-pandemic, surgical care for patients with benign conditions was delayed, with unknown consequences for patient-reported outcomes and disease-related morbidity. (1) This real-world scenario provides a unique opportunity to evaluate the impact of surgical capacity scarcity on the management of the most common benign surgical conditions—inguinal hernia and gallstone disease.

Inguinal hernia repair (IHR) and laparoscopic cholecystectomy (LC) are two of the most common general surgical procedures worldwide, performed over 140,000 times every year in the United Kingdom (UK) and nearly 50,000 in the Netherlands. (2-5) These procedures are primarily performed electively to relieve symptoms and prevent disease-related complications. Both conditions have a benign natural course with low annual complication rates of 0.4% for inguinal hernias (e.g. incarceration, strangulation) and 0.3% for gallstone disease (e.g. cholecystitis, biliary pancreatitis). (6-8) However, delayed surgery may lead to lingering symptoms and, in some cases, increased disease-related morbidity and even surgical complications. Recognizing these consequences is crucial for prioritizing surgical care in times of scarcity.

The COVID-19 pandemic significantly disrupted surgical care worldwide, leading to the prioritization of malignant over benign conditions due to limited healthcare resources. (1) No national guidelines for hospital-level care were issued. Hospitals implemented crisis strategies, including the cancellation or postponement of outpatient appointments, reallocation of personnel, and repurposing of operating theatres as intensive care units. Within surgical departments, attending surgeons were generally not redeployed, whereas residents were reassigned to other wards. Worldwide more than 2 million surgeries per week were cancelled during the first wave of this pandemic, and most of them comprised elective surgeries. (9) Elective procedures for benign conditions were either canceled or severely delayed with unknown impact on disease related complications. (10)

Previous studies, including the work by de Graaf et al., have highlighted the impact of COVID-19 on number of performed elective surgical procedures. However, there is lack of data addressing disease-related morbidity in benign surgical conditions if capacity is constrained. (1) The aim of this study was to evaluate the impact of the COVID-pandemic on benign surgical care for patients with gallstone disease or an inguinal hernia. Therefore, we compared the disease-related- and surgical complications between the COVID period and a pre-COVID reference period.

METHODS

Study design and Participants

This multicentre historical cohort study was conducted in three Dutch hospitals; one academic medical centre (Radboudumc Nijmegen) and two teaching hospitals (CWZ hospital, Nijmegen and Maasziekenhuis Pantein, Boxmeer). Annual admissions per hospital range from approximately 7,000 to 22,500, with surgical volumes ranging from several thousand to approximately 30,000 procedures per hospital per year. All patients aged 18 or older with a new referral to the surgical outpatient clinic or emergency department with an assigned Diagnosis Related Groups (DRG) code for any gallstone-related disease or inguinal hernia between March and December 2019 (the reference period) and March to December 2020 (the COVID period) were included. In the Netherlands, Diagnosis Related Groups (DRG) codes, known as Diagnosis Treatment Combinations (DBCs), are allocated to every patient who presents at a hospital. DRGs consist of a specific diagnosis and the corresponding treatment pathway, covering the entire patient care trajectory from diagnosis to follow-up. Data collection occurred in two phases between July and December 2021: 1) extracting data using DRG registries and 2) evaluating individual patient records.

Ethical approval was provided by the Radboudumc medical ethical committee (registration number 2020-6739) and the boards of directors of the participating hospitals. The requirement for written informed consent was waived due to the retrospective nature of the study. This research was performed in accordance with the ethical standards of the updated Helsinki Declaration of 2013.

Outcomes and variables

The primary outcome of this study was the rate of disease-related complications. The disease-related complications assessed in this study were determined by collaborating surgeons and were listed in Table 1. Gallstone disease was categorized as uncomplicated gallstone disease (cholecystolithiasis) or complicated gallstone disease (acute cholecystitis, choledocholithiasis, biliary pancreatitis, cholangitis, biliary colic with hospital admission). Inguinal hernias were categorized as uncomplicated inguinal hernias or complicated inguinal hernias (inguinal hernia with incarceration, strangulation or ileus).

Table 1, Overview of complications considered

Disease-related complications	
Gallstone disease	Uncomplicated gallstone disease: symptomatic cholecystolithiasis. Complicated gallstone disease: acute cholecystitis, choledocholithiasis, biliary pancreatitis, cholangitis, biliary colic with hospital admission.
Inguinal hernia	Incarcerated hernia, Strangulation, Ileus, Hydrocele
Surgery-related complications	
General	Wound infection, postoperative bleeding, length of stay, postoperative readmission in ED, postoperative readmission in hospital, abscess (wound or abdominal)
Gallstone disease	Reintervention (percutaneous drainage, ERCP, reoperation), bile duct injury (Strasberg)
Inguinal hernia	Visceral resection (omentum, intestine, appendix), reoperation, hernia recurrence within 6 months

Secondary outcomes included surgery rates, the method of first admission (outpatient clinic, emergency department, or clinical consultation), time to surgery, surgical complications within 30 days post-surgery, length of hospital stay, and hospital readmissions within six months of follow-up. Data obtained from the DRG-registries (first phase) include: DRG-code, date of first presentation, way of admission (i.e. outpatient clinic, Emergency Department (ED), other), number of surgeries performed, date of surgery, admission and duration of admission, readmission and duration of readmission. Secondly, individual medical records were reviewed during phase 2 if a patient met one or more of the following criteria: admission through the ED, surgery in an emergency setting (time interval between diagnosis and the operation shorter than 72 hours), prolonged hospital stay (>24 hours), and readmission. To minimize measurement bias, these variables were predefined by two surgeons, two researchers, one methodologist and two data-managers. The following data were obtained from individual medical records: patient characteristics (such as gender, age, BMI), type of disease-related complications (table 1), and surgical complications and related interventions. Surgical complications were scored in accordance with the Clavien-Dindo Classification. (11)

Statistical analyses

The COVID-19 period and the reference period were compared with respect to the primary and secondary outcomes. Dichotomous outcomes were expressed as frequencies and proportions. Continuous outcomes were presented as mean with standard deviation when normally distributed and median with range or interquartile range when data were not normally distributed. (12) Statistical significance of differences in proportions of diagnoses, operation rate, and disease- or surgery-related complications was

assessed using the chi-square test. Differences in time to surgery was assessed using the Mann-Whitney U test. P-values less than 0.05 were considered statistically significant. Subgroup analysis included separate analyses in patients with uncomplicated gallstone disease and those with complicated disease (e.g., cholecystitis), as these represent distinct clinical entities. RDG registry data were complete; however, missing data for variables assessed through individual patient record review are reported in the respective tables. Statistical analyses were performed using complete case analysis. IBM SPSS statistical software version 25.0 (SPSS Inc., Chicago, IL) was used for all analyses.

RESULTS

In total 3,083 patients were included during the study period, 1,624 in the reference period and 1,459 during the COVID-period. Figure 1 shows an overview of included patients, and Figure 2 illustrates a decrease in patients referred to hospital during the COVID-period, mainly during the first wave (March-May 2020).

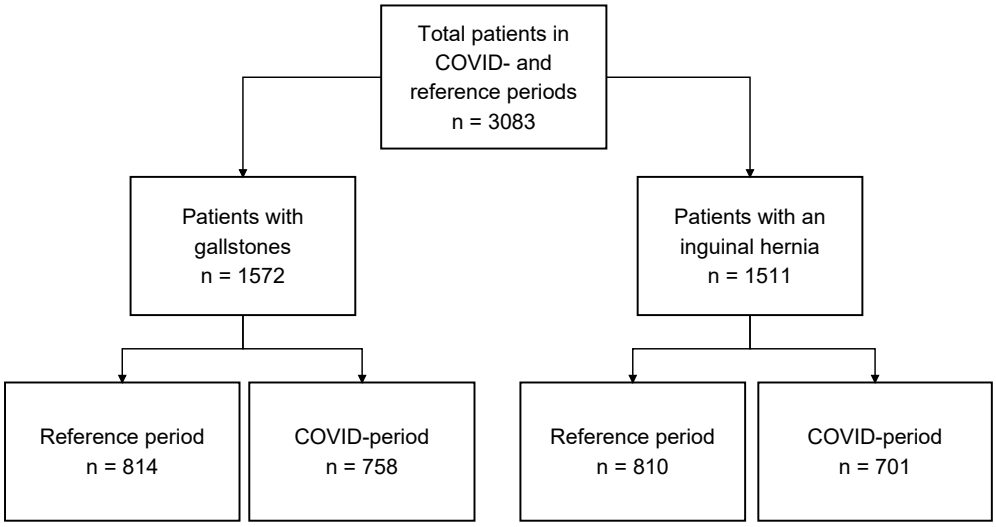

Figure 1, Flowchart of inclusions. The reference period was from March-December 2019 and the COVID-period from March-December 2020

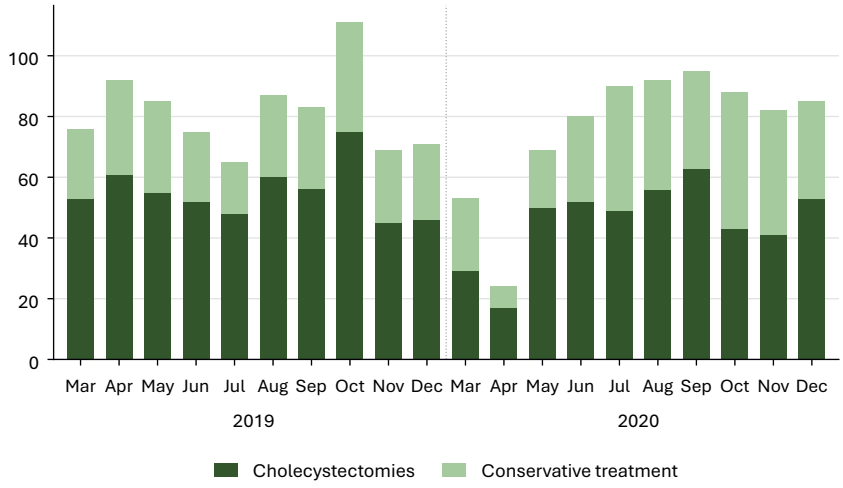

Figure 2A Monthly number of patients with gallstone disease and number of cholecystectomies

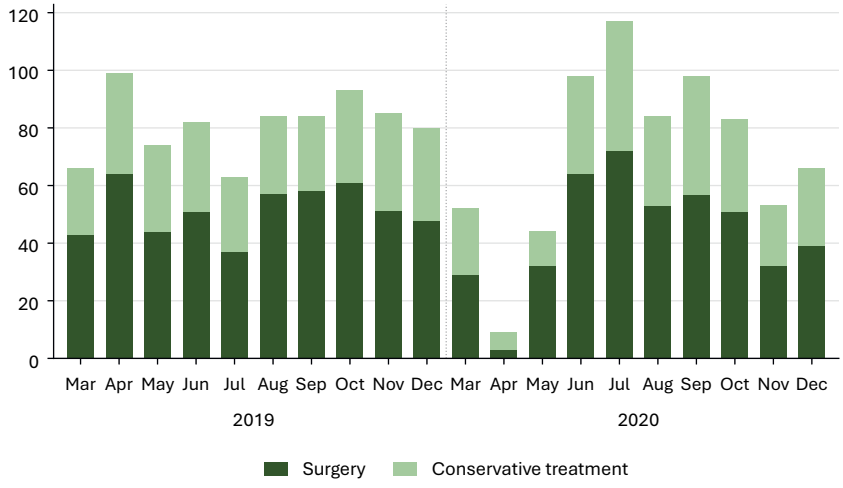

Figure 2B Monthly number of patients with an inguinal hernia and number of inguinal hernia repairs

Patient characteristics treatment in patients with gallstones.

Table 2 provides an overview of patients with gallstone disease. In total, 1,572 patients with gallstone disease were included: 814 in the reference period in 2019 and 758 during the COVID-period in 2020. Of these, 63.9% (1,004/1,572) underwent LC after a median period of 28.0 days. Readmission after diagnosis occurred in 4.6% (73/1571) of patients, of whom 91.8% (67/73) were readmitted after LC.

Among 1,572 patients with gallstone disease, 75.1% (1,180) were diagnosed with cholecystolithiasis, 9.1% (301/1,572) with cholecystitis, 2.2% (35/1,572) with choledocholithiasis, 2.0% (31/1,572) with cholangitis, and 1.6% (25/1,572) with biliary pancreatitis (Table 2). In total, 24.9% (392/1,572) were diagnosed with complicated gallstone disease.

Detailed information on the number of cholecystectomies performed for uncomplicated versus complicated gallstone disease, and their distribution across the two study periods, is provided in the Supplementary Table 1. Among patients with cholecystolithiasis, 57.4% (677/1,180) underwent LC. The proportion of patients undergoing LC was significantly higher during the reference period compared to the COVID period (61.9% [395/638] vs. 52.0% [282/542]; P < 0.001). The median time to surgery increased from 32 days in the reference period to 49 days during the COVID-period, representing a 37% increase (p = 0.009). Additionally, 2.5% (25/888) of patients initially referred for cholecystolithiasis developed acute cholecystitis.

The proportion of patients diagnosed with complicated gallstone disease was significantly lower in the reference period: 21.6% (176/814) vs. 28.5% (216/758) during the COVID period, reflecting a 24.2% relative increase (P = 0.002). This increase was accompanied by a significantly higher rate of cholangitis in the COVID period (1.2% [10/814] vs. 2.8% [21/758]; P = 0.02). Among patients with acute cholecystitis, a higher proportion underwent LC in the reference period than during the COVID period (91.5% [130/142] vs. 83.6% [133/159]; P = 0.04). Furthermore, significantly fewer patients with acute cholecystitis underwent surgery more than 7 days after admission in the reference period compared to the COVID period (13.8% [18/130] vs. 25.6% [32/133]; P = 0.02).

Surgical complications occurred in 13.6% (136/1,004) of patients who underwent LC, of whom 7.2% had complications classified as Clavien-Dindo grade ≥ III, requiring invasive intervention. No significant difference in rate in surgical complications Clavien-Dindo ≥ 3 was observed between the reference and COVID period (7.3% [33/454] vs. 7.1% [39/550]; P = 1.0). Bile duct injuries occurred in 1.5% (15/1,004) (Table 2). The specific grade of bile duct injury was not recorded in this study; however, 2 patients experienced bile duct injury-related mortality, 2 underwent surgical reintervention, and 8 received endoscopic retrograde cholangiopancreatography (ERCP) with or without stent placement.

Table 2, Characteristics and follow-up of patients with gallstone disease

	Total N = 1572	Reference period N = 814	COVID-period N = 758	P-value
Sex, n female (%)	572 (60.5)	306 (62.1)*	266 (58.8)†	0.31
Age, mean (SD)	58.4 (17.6)	57.1 (17.6)*	59.7 (17.5)†	**0.03**
BMI, mean (SD)	28.3 (5.7)	28.1 (5.8)‡	28.4 (5.5)§	0.57
Presentation outpatient clinic, n (%)	888 (56.5)	482 (59.2)	406 (53.6)	**0.02**
Presentation ED, n (%)	533 (33.9)	271 (33.3)	262 (34.6)	0.59
Cholecystectomy, yes (%)	1004 (63.9)	551 (67.7)	453 (59.8)	**0.001**
Time to surgery in days, median (IQR)	28.0 (57.0)	22.0 (46.0)	32.5 (74.8)	**<.001**
Surgical complications, n (%)	136 (13.6)	82 (14.9)	54 (11.9)	0.18
CDC ≥ 3, n (%)	72 (7.2)	39 (7.1)	33 (7.3)	0.90
Bile duct injury, n (%)	15 (1.5)	7 (1.3)	8 (1.8)	0.52
Uncomplicated gallstone disease, n (%)	1180 (75.1)	638 (78.4)	542 (71.5)	**0.002**
Complicated gallstone disease, n (%)	392 (24.9)	176 (21.6)	216 (28.5)	**0.002**
Admission for biliary colic, n (%)	11 (0.7)	4 (0.5)	7 (0.9)	0.30
Choledocholithiasis, n (%)	35 (2.2)	14 (1.7)	21 (2.8)	0.16
Cholecystitis, n (%)	301 (19.1)	142 (17.4)	159 (21.0)	0.08
Cholangitis, n (%)	31 (2.0)	10 (1.2)	21 (2.8)	**0.03**
Biliary pancreatitis, n (%)	25 (1.6)	10 (1.2)	15 (2.0)	0.24
Hospital admission, yes (%)	998 (63.5)	560 (68.8)	438 (57.8)	**<.001**
Hospital stay in days, median (IQR)	0.84 (1.02)	0.83 (0.90)	0.86 (1.09)	0.14
Readmissions, n (%)	73 (4.6)	39 (4.8)	34 (4.5)	0.77

* 321 missings † 303 missings ‡ 596 missings § 568 missings

Patient characteristics, referral pattern and treatment in patients with an inguinal hernia.

Table 3 provides an overview of patients with an inguinal hernia. In total, 1,511 patients with an inguinal hernia were included: 810 in the reference period and 701 during the COVID-period. Of these, 62.6% (946/1,511) of patients received an inguinal hernia repair after a median period of 53.0 days.

The majority of patients, 95.4% (1,376/1,442) patients were diagnosed with an uncomplicated symptomatic inguinal hernia, while 4.6% (69/1,511) patients had either incarceration or incarceration with strangulation. There was no significant difference in the rate of patients with inguinal hernia-related complications between the reference period and the COVID-period (3.7% [31/810] vs. 5.4% [38/701]; p = 0.14). During follow-up 3.1% (57/1,511) of patients were readmitted.

Most patients with an incarcerated or strangulated inguinal hernia were diagnosed during initial visit to the emergency department (87.0%) (Supplementary Table 2). After initial

assessment for an uncomplicated inguinal hernia, 0.6% (9/1,387) patients developed a hernia-related complication. Patients receiving surgery for an uncomplicated inguinal hernia did not differ significantly between the reference period and the COVID period (62.3% [485/779] vs. 60.6% [402/663], p = 0.53), but 15.7% less patients received inguinal hernia repair in the case of a complicated inguinal hernia (78.9% [30/38] vs. 93.5% [29/31], p = 0.09).

Surgical complications occurred in 4.3% of hernia repairs (41/946), with 2.9% of these being Clavien-Dindo ≥ 3, requiring invasive intervention. No significant difference in rate in surgical complications Clavien-Dindo ≥ 3 was observed between the reference and COVID period (11.8% [4/38] vs. 20.7% [6/31]; p = 0.33).

Table 3, Characteristics and follow-up of patients with an inguinal hernia

	Total N = 1511	Reference period N = 810	COVID-period N = 701	P-value
Sex, n male (%)	541 (89.7)	294 (87.0)*	247 (93.2)†	**0.012**
Age, mean (SD)	61.5 (16.4)	62.6 (15.6)*	60.1 (17.2)†	0.056
BMI, mean (SD)	25.3 (3.2)	25.3 (3.1)‡	25.3 (3.4)§	0.996
Presentation outpatient clinic, n (%)	1402 (92.8)	756 (93.3)	646 (92.2)	0.38
Presentation ED, n (%)	104 (6.9)	51 (6.3)	53 (7.6)	0.333
Inguinal hernia repair, yes (%)	946 (62.6)	514 (63.5)	432 (61.6)	0.463
Time to surgery in days, median (IQR)	53.0 (56.0)	42.0 (50.25)	67.0 (57.75)	**<.001**
Surgical complications, n (%)	61 (6.1)	40 (7.3)	21 (4.7)	0.095
CDC ≥ 3, n (%)	28 (2.8)	14 (2.6)	14 (3.2)	0.568
Hernia-related complication, n (%)	69 (4.6)	31 (3.7)	38 (5.4)	0.139
Incarceration, n (%)	54 (3.6)	22 (2.7)	32 (4.6)	0.054
Incarceration with strangulation or ileus, n (%)	14 (0.9)	8 (1.0)	6 (0.9)	0.79
Hospital admission, yes (%)	985 (65.2)	541 (66.8)	444 (63.3)	0.160
Hospital stay in days, median (IQR)	0.31 (0.11)	0.32 (0.12)	0.31 (0.10)	0.301
Readmissions, n (%)	57 (3.1)	30 (3.1)	27 (3.0)	0.97

**472 missings † 436 missings ‡ 592 missings § 529 missings*

DISCUSSION

This multicenter cohort study describes the effects of the COVID-19 period, marked by constrained healthcare resources and limited surgical capacity, on disease- management and related morbidity in surgical patients with a benign condition. During this period, more patients were diagnosed with complicated gallstone disease, and both uncomplicated and complicated gallstone disease were more frequently managed conservatively. This trend was not observed for inguinal hernia-related complications during

the COVID-19 period. Additionally, there were significant delays in the timing of surgical care for patients with gallstone disease or an inguinal hernia, highlight the consequences of limited surgical capacity on the management of benign conditions.

The observation of increased conservative management and delayed surgical intervention in this study aligns with international data showing that, during the first wave of the COVID-19 pandemic, surgical care for benign conditions was reduced more extensively than for malignant conditions. A global modelling study predicted an overall cancellation rate of 72.3%, with benign diseases being most affected (81.7%), while surgeries for malignant conditions were relatively prioritized (37.7%). (9) In the Netherlands, De Graaff et al. showed a decrease of elective surgeries of up to 50% in March, April and May 2020. (1) In these critical months, we found similar reductions, with the biggest drop in referred patients occurring in April 2020.

The present study observed a 24% increase in presentations of patients with complicated gallstone disease, which contrasts with previous literature that did not report such an increase during the pandemic. (13-15) Several hypotheses can be proposed. Firstly, the high proportion of complicated gallstone disease observed during the COVID period may reflect a selective presentation of patients with more severe disease, driven by delays in presentation and treatment resulting from COVID-related disruptions across the healthcare system. The current cohort showed a marked reduction in hospital admissions for both cholecystolithiasis and inguinal hernia during the COVID period. This observation aligns with previous studies showing changes in healthcare-seeking behavior, partly due to fear of COVID-19 transmission, leading to delayed treatment. (16, 17) Data from primary care further supports this, showing a 25% reduction in consultation by the general practitioner during the critical months of 2020 when compared to the same period in 2019. For non-urgent consultations, this reduction reached up to 60%. (16) Given that under normal circumstances only 60% of patients with biliary colic seek care from a general practitioner, it is plausible that healthcare seeking behavior was further reduced during the pandemic. (18) Additionally, studies show that surgical priorities changed with greater emphasis on conservative management and maximization of theatre availability for acute procedures, contribution to the selection of more severe cases. (19) Consequently, delayed patient presentation and shifts in surgical priority may have contributed to a selective presentation of more severe cases, rather than an absolute increase of complicated gallstone disease, during the COVID-19 period.

Secondly, delays in surgery for benign conditions may lead to a true increase in disease-related complications over time. However, these explanations, seem less likely for several reasons. Firstly, the risk of developing complicated gallstone disease in conservatively treated patients with cholecystolithiasis is relatively low. In the current study, only 6.8% of patients with cholecystolithiasis presenting at the outpatient clinic devel-

oped a gallstone-related complication. Moreover, more than half of patients with acute cholecystitis do not experience a 'warning' biliary colic, suggesting that many cases of acute cholecystitis are primarily presented to the emergency room and could not have been prevented by timely referral and surgery for cholecystolithiasis. (18) Furthermore, recent trials with follow-up periods of up to 2-5 years indicate that restrictively selected or conservatively treated patients do not have an increased risk of complicated gallstone disease. (20, 21) However, more long-term follow-up studies investigating conservative management for cholecystolithiasis are needed to confirm safety.

For inguinal hernias the COVID period did not affect disease-related complications or surgical complications, which aligns with results from previous studies. (17, 22-24) All these studies however, only included patients who received a hernia repair and failed to include non-surgical patients. Previous studies found similar rates of incarceration between 0.6% and 4.5% as in the current cohort. (25-27)

Clinical implications

These results provide valuable insights not only in the context of a future pandemic, but also for routine surgical practice given the lasting scarcity healthcare resources. During the COVID-19 pandemic, there was little evidence-based guidance for the allocation of scarce surgical capacity. In this context, reevaluating surgical indications is becoming increasingly important to ensure allocation of capacity to high-value procedures. Assessing the efficacy and added value of surgical interventions—particularly in terms of disease morbidity and quality of life—is therefore warranted to enable evidence-based prioritization of limited surgical resources. Secondly, patient selection and exploring non-surgical treatment options is essential. In the management of gallstone disease, growing evidence supports conservative approaches as safe and effective alternatives to surgery. (20, 21) The use of decision aids may help guide the consideration of conservative treatments in shared decision-making processes. The effects of shared decision-making, supported by decision aids, are currently being studied in the multicenter E-valuAID trial, which includes patients with gallstone disease, inguinal hernia, and knee or hip osteoarthritis. (28)

Strengths and limitations

This study has multiple strengths. First, a large group of consecutive patients with two different diagnoses was included from three separate hospitals. Second, in comparison to existing literature, our study not only quantified the effect of the pandemic on provided treatment by also describes the impact on disease-related complications. Third, collection of data was standardized for both conditions.

This study also has some limitations. Firstly, some complications may have been missed

due to selection criteria for medical record review, potentially introducing sampling bias. However, the criteria were designed to be lenient, minimizing the chance of missing complications. Secondly, complications were not tracked prospectively but extracted from registration data, which may have led to underreporting. Moreover, the evaluation was limited to disease- and surgery-related complications. Non-surgical complications (e.g. cardiovascular or pulmonary events) were not assessed. Thirdly, this registry-based study aimed to descriptively report differences between two periods rather than assess associations, therefore no adjustment for confounding was done by multivariable analysis. Lastly, the retrospective design precluded the use of patient reported outcome measures.

Conclusion

During the COVID period, there was a decrease in number of cholecystectomies performed and a 24% increase in diagnoses of complicated gallstone disease, but no difference in surgical complications. For inguinal hernias, no significant difference in disease-related complications was found.

SUPPLEMENTARY TABLES

Supplementary Table 1. Comparison of the reference period and the COVID period in patients with uncomplicated or complicated gallstone disease.

	Uncomplicated gallstone disease (N = 1180)			**Cholecystitis (N = 301)**		
	Reference N = 638	**COVID N = 542**	**p**	**Reference N = 142**	**COVID N = 159**	**P**
Sex, n female (%)	372 (67.3)			142 (47.2)		
	213 (67.2)	159 (67.4)	0.96	71 (50.0)	71 (44.7)	0.35
Age, mean (SD)	55.2 (18.0)			62.5 (16.0)		
	53.8 (17.7)	57.0 (18.2)	0.04	63.2 (15.9)	61.9 (16.1)	0.49
BMI, mean (SD)	28.3 (5.7)			28.1 (5.7)		
	28.3 (5.8)	28.3 (5.7)	0.93	27.9 (6.1)	28.4 (5.2)	0.70
Presentation ED, n (%)	242 (20.5)			255 (84.7)		
	136 (21.3)	106 (19.6)	0.46	121 (85.2)	134 (84.3)	0.82
Presentation outpatient clinic, n (%)	828 (70.2)			22 (7.3)		
	461 (72.3)	367 (67.7)	0.09	9 (6.3)	13 (8.2)	0.54
Cholecystectomy, yes (%)	677 (57.4)			263 (87.4)		
	395 (61.9)	282 (52.0)	**<.001**	130 (91.5)	133 (83.6)	**0.04**
Time to surgery in days, median (IQR)	37 (50.5)			1.0 (2.0)		
	32.0 (40.0)	49.0 (60.5)	**<.001**	1.0 (2.0)	1.0 (8.0)	0.23
Surgical complications, n (%)	51 (7.5)			67 (25.5)		
	34 (8.6)	17 (6.0)	0.21	39 (30.0)	28 (21.1)	0.10
CDC ≥ 3, n (%)	29 (4.3)			30 (11.4)		
	17 (4.3)	12 (4.3)	0.98	15 (11.5)	15 (11.3)	0.95
Bile duct injury, n (%)	8 (1.2)			4 (1.5)		
	4 (1.0)	4 (1.4)	0.63	1 (0.8)	3 (2.3)	0.33
Hospital admission, yes (%)	675 (57.2)			258 (85.7)		
	402 (63.0)	273 (50.4)	**<.001**	129 (90.8)	129 (81.1)	**0.02**
Hospital stay in days, median (IQR)	0.4 (0.7)					

	Uncomplicated gallstone disease (N = 1180)			Cholecystitis (N = 301)		
	Reference N = 638	COVID N = 542	p	Reference N = 142	COVID N = 159	P
	0.43 (0.67)	0.43 (0.6)	0.97	2.6 (3.0)	1.7 (2.3)	**0.04**
Readmissions, n (%)	26 (2.2)			24 (8.0)		
	20 (3.1)	6 (1.1)	**0.02**	8 (5.6)	16 (10.1)	0.16

Supplementary Table 2. Comparison of the reference period and the COVID period in patients with an uncomplicated or a complicated inguinal hernia

	Uncomplicated inguinal hernia (N = 1442)			Complicated inguinal hernia (N = 69)		
	Reference N = 779	COVID N = 663	p	Reference N = 31	COVID N = 38	P
Sex, n female (%)	53 (9.9)			9 (13.0)		
	37 (12.1)	16 (7.0)	0.06	7 (22.6)	2 (5.3)	**0.03**
Age, mean (SD)	60.4 (16.2)			70.4 (14.8)		
	61.8 (15.8)	58.4 (16.7)	**0.02**	70.9 (10.8)	70.0 (17.6)	0.79
BMI, mean (SD)	25.4 (3.2)			24.9 (3.2)		
	25.3 (3.1)	25.4 (3.4)	0.86	25.3 (2.8)	24.6 (3.6)	0.65
Presentation ED, n (%)	45 (3.1)			59 (85.5)		
	23 (3.0)	22 (3.3)	0.69	28 (90.3)	31 (81.6)	0.31
Presentation outpatient clinic, n (%)	1393 (96.6)			9 (13.0)		
	753 (96.7)	640 (96.5)	0.89	3 (9.7)	6 (15.8)	0.45
Inguinal hernia repair, yes (%)	887 (61.5)			59 (85.5)		
	485 (62.3)	402 (60.6)	0.53	29 (93.5)	30 (78.9)	0.09
Time to surgery in days, median (IQR)	54.0 (55.0)			18.5 (57.5)		
	49.9 (38.1)	70.0 (39.9)	**<.001**	38.6 (49.4)	31.1 (35.4)	0.58
Surgical complications, n (%)	44 (4.7)			17 (27.0)		
	30 (5.8)	14 (3.4)	0.09	10 (34.5)	7 (20.6)	0.22
CDC ≥ 3, n (%)	18 (1.9)			10 (15.9)		
	8 (1.5%)	10 (2.4)	0.32	6 (20.7)	4 (11.8)	0.33
Hospital admission, yes (%)	925 (64.1)			60 (87.0)		
	512 (65.7)	413 (62.3)	0.18	29 (93.5)	31 (81.6)	0.14
Hospital stay in days, median (IQR)	0.3 (0.1)			1.0 (2.6)		
	0.5 (1.2)	0.4 (0.5)	0.10	2.0 (3.0)	5.7 (14.2)	0.20
Readmissions, n (%)	35 (2.4)			8 (11.6)		
	18 (2.3)	17 (2.6)	0.76	5 (16.1)	3 (7.9)	0.29

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CHAPTER

5

Persistent and new-onset symptoms after cholecystectomy in patients with uncomplicated symptomatic cholecystolithiasis: a post-hoc analysis of two prospective clinical trials.

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Surgery 2023

ABSTRACT

BACKGROUND Laparoscopic cholecystectomy is the gold standard for treating biliary colic in patients with gallstones, but post-cholecystectomy abdominal pain is commonly reported. This study aims to investigate which symptoms are likely to persist and which symptoms may newly develop after a cholecystectomy.

METHODS Patients from two previous prospective trials who underwent a laparoscopic cholecystectomy for symptomatic cholecystolithiasis were included. Patients completed questionnaires on pain and gastrointestinal symptoms prior to surgery and at 6 months follow-up. The prevalence of persistent and new-onset abdominal symptoms was evaluated.

RESULTS A total of 820 patients received cholecystectomy and were included, 75.4% female (n= 616/820) mean age 49.4 years (SD 13.7). At baseline, 74.1% (n= 608/820) of patients met all criteria for a biliary colic. Cholecystectomy successfully resolved biliary colic in 94.8% (n= 327/345) of patients, but 36.5% (n= 299/820) of patients reported persistent abdominal pain after 6 months of follow-up. The prevalence of most abdominal symptoms reduced significantly. Symptoms like flatulence (17.8%, n= 146/820) or restricted eating (14.5%, n= 119/820) persisted most often. New-onset symptoms were frequent bowel movements (9.6%, n= 79/820), bowel urgency (8.5%, n= 70/820) and new-onset diarrhea (8.4%, 69/820).

CONCLUSIONS: Post-cholecystectomy symptoms are mainly flatulence, frequent bowel movements, and restricted eating.. Newly reported symptoms are mainly frequent bowel movements, bowel urgency and diarrhea. Present findings give clinical guidance in informing, managing and treating patients with symptoms after cholecystectomy.

INTRODUCTION

Cholecystectomy is the gold standard for treating symptomatic cholecystolithiasis, resulting in over 335,000 surgeries annually in the United States (US) and over 23,000 surgeries in the Netherlands. (1, 2) Cholecystectomy effectively alleviates biliary colic. However, up to 40% of patients have persistent abdominal pain. (3) A cross-sectional study showed that persistent abdominal pain results in additional medical costs and costs of sick leave of 20% of the initial costs of cholecystectomy. (4) A review identified different groups of patients with post-operative pain: 1. surgery-related complications, 2. residual and/or newly formed gallstones, 3. psychological distress, 4. sphincter of Oddi dysfunction, 5. physiological changes (e.g. altered bile acid metabolism) and 6. pre-existing functional gastrointestinal disorders as irritable bowel syndrome and functional dyspepsia, the latter of which appears the most important factor. (5) In 2013, another review determined the incidence of persistent (such as diarrhea (26-85%) and constipation (57-76%)) and de novo symptoms (flatulence (0-62%)). (6) However, prospective data on the prevalence of preoperative and postoperative symptoms are lacking and vary considerably across studies.

Because of a lack of adequate preoperative screening for disorders unrelated to gallstones prior to cholecystectomy, patients with persisting abdominal complaints are often referred to a gastroenterologist. Prospective data would help to determine the extent of this group of patients with preoperative unrelated disorders and postoperative complaints, and may aid in patient selection for cholecystectomy and post-operative management. Therefore, data from two prospective trials, which included patients who underwent cholecystectomy, are analyzed in the present study. These trials were 1) the SECURE-trial, a randomized controlled trial to compare the non-inferiority of a restrictive strategy in selection for laparoscopic cholecystectomy (LC) with usual care, and 2) the SUCCESS-trial, a observational cohort study to develop and validate a decision-tool to select patients for cholecystectomy. This post-hoc analysis aims to determine which symptoms are present pre-operatively and persist after cholecystectomy and which symptoms may arise de novo.

METHODS

Study design and population

The present study has been structured in accordance with the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines. (7) This study combines data from two prospective multicenter studies: 1. The SECURE-trial, conducted between 2014-2017, and 2. the SUCCESS-trial, conducted between 2017-2019. The

SECURE-trial was a randomized controlled trial performed in 24 hospitals in the Netherlands to compare the non-inferiority of a restrictive strategy in selection for (LC) with usual care. (3) The restrictive strategy meant that patients only received LC if they met all ROME-criteria (biliary colic with pain radiation to the back and a positive response to simple analgesics). The SUCCESS-trial was performed in 7 hospitals in the Netherlands and was executed to develop and validate a decision-tool to select patients for cholecystectomy. (8) In- and exclusion criteria in both trials were similar; both trials included patients between 18 to 95 years of age presenting at the surgical outpatient clinic with abdominal pain and ultrasonically confirmed gallstones or sludge. Exclusion criteria were: pregnancy, history of complicated cholecystolithiasis, an indication for primary open cholecystectomy, an American Society of Anesthesiologists physical status classification (ASA) of III and IV, a history of current malignancy, an expected life span of fewer than 12 months, known liver cirrhosis, cognitive disorders that predispose unreliable questionnaire responses and insufficient knowledge of the Dutch language. For this post-hoc analysis, only patients were included who underwent surgery within 6 months after inclusion and completed questionnaires at baseline and follow-up. Responders and non-responders were compared in terms of age, sex and body mass index (BMI).

Questionnaires

Four validated Dutch questionnaires were used prior to surgery and after 6 months follow-up in both studies:

The Izbicki Pain Score (IPS); is a questionnaire developed for patients with upper abdominal pain. It consists of four questions on pain severity, frequency, use of analgesics and disease-related work disability. The questionnaire also contains a separate Visual Analogue Scale (VAS) for pain severity, from 0 (no pain) to 10 (worst possible pain). (9) Total scores range from 0-100, with higher scores indicating more severe pain.

The Gallstone Symptom List (GSL); is a questionnaire designed to assess pain associated with symptomatic cholecystolithiasis. It consists of four questions on pain duration, intensity, frequency and response to analgesics. These questions are scored on a 5-point Likert scale, from 0 (best appraisal) to 4 (worst appraisal). (10)

The GastroIntestinal Quality of Life Index (GIQLI); Gastrointestinal symptoms were evaluated using the Gastrointestinal Quality of Life Index (GIQLI). This questionnaire consists of thirty-six questions in five domains. These symptoms can be scored on a 5-point Likert scale, ranging from 0 (worst score) to 4 points (best score). (11)

ROME-criteria; The ROME-criteria are widely used to define biliary colic. It consists of three criteria: severe pain attacks in the epigastrium or right upper quadrant of the abdomen, lasting over 15-30 minutes. In both studies, two additional questions were added

to the three original criteria: pain radiating to the back and positive effect of analgesics. (12) In the SECURE-trial, this questionnaire was not sent after 6 months of follow-up.

An overview of the questionnaires is presented in Table 1.

Table 1. Overview of questionnaires

	No. of questions	Range per item	Range of total score
Izbicki Pain Score (IPS) (9)	4	0-100	0-100
Gallstone Symptom List (GSL)(10)	5	0-4	0-16
GastroIntestinal Quality of Life Index (GIQLI) (11)	36	0-4	0-144
ROME-criteria(12)	5	0-1	0-5

Variables and outcomes

The prevalence of symptoms was evaluated at baseline (at inclusion) and after six months of follow-up. For this, cut-off points on the 5-point Likert scales were selected. (13) Symptoms were considered to be present if patients indicated a score of ≥ 2 on the GSL and ≤ 2 on the GIQLI (equivalent to symptom being present some-, most-, or all of the time). A biliary colic was considered to be present if patients fulfilled all three ROME-criteria: Pain in attacks, located in the upper or upper right quadrant, lasting over 15-30 minutes. Pain-free was defined as an IPS ≤10 and a VAS ≤4, in line with previous studies. (3, 8) Pain and symptoms were defined *persistent* if present at both baseline and after six months of follow-up. Symptoms were defined *new-onset* if absent at baseline and present at six months of follow-up. Outcomes will be visualized in a heatmap to illustrate the magnitude of symptoms in colors (ranging from red for the highest prevalence in a group of patients to green for the lowest prevalence). Surgical complications were scored in accordance with the Clavien-Dindo classification (CDC). (14) CDC scores of ≥ 3 were considered as a major complication.

Statistical analyses

To evaluate symptoms before and after LC, items in the questionnaires about symptoms (i.e. pain-attacks and abdominal symptoms), originally scored on 5-point scales, were transformed into binary variables as described above. These binary variables and the ROME-criteria were used to evaluate prevalence of symptoms at baseline and after 6 months of follow-up, presented by proportions (%). Comparison of the prevalence of these variables at baseline and after follow-up was done using the $\chi 2$ test. Categorical data (i.e. patient sex, history of abdominal surgery) were summarized by frequencies and proportions. Continuous data (i.e. age, BMI, VAS pain score) were presented as mean

with standard deviation (SD) when normally distributed, or as median with interquartile range (IQR) when non-normally distributed. To assess normality of data distributions, histograms were plotted and examined.

To assess attrition bias of patients lost to follow-up, clinical characteristics of responders and non-responders to the questionnaires were compared (i.e. age, VAS pain score, sex, BMI). Comparison of clinical characteristics between responders and non-responders to the questionnaires was done using the $\chi 2$ test for categorical variables, student's t-test for continuous variables with normal distribution and Mann–Whitney U-test for non-normally distributed variables. A p-value of less than 0.05 indicated statistical significance. Missing data on questionnaires were excluded from analyses. Data analyses were performed using SPSS software Version 27.0 (SPSS, Chicago, Illinois, USA).

RESULTS

Patients and baseline characteristics

Patients were included between February 2014 and April 2017 in the SECURE-trial (n= 1067), and between October 2017 and June 2019 in the SUCCESS-trial (n= 494). A total of 1101 gallstone patients underwent LC (n=714 in the SECURE-trial; n=387 in the SUCCESS-trial) and were eligible for inclusion, of whom 281 (25.5%) did not respond to all surveys (n=239 in SECURE-trial; n=42 in SUCCES-trial). In total 820 patients were included (Figure 1).

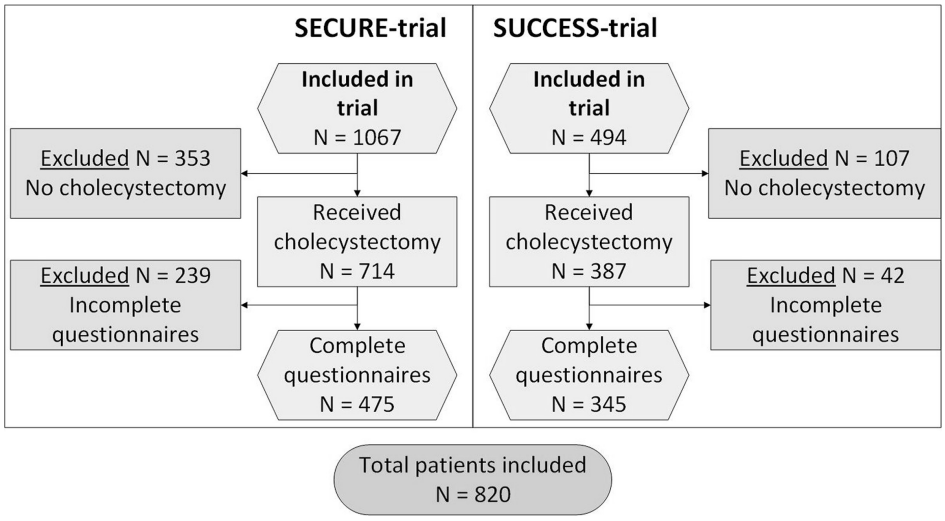

Figure 1. Flowchart of patient inclusion.

Between responders and non-responders no significant differences were found in terms of sex and BMI, but responders were older (mean age 49.3 (SD ± 13.7) vs. 44.3 (SD ± 13.3) years, $P < .001$) and reported more severe pain at baseline (median VAS pain score 8.0 (IQR 2.55) vs. 8.0 (IQR 2.38), p = 0.048). Of the responders, 75.7% (n=621) were female and mean BMI was 28.6 (SD ± 5.0) (Table 2).

Table 2. Baseline characteristics

Baseline characteristics	Total group (N=820)
Sex, female, n (%)	621 (75.7)
Age, mean (SD)	49.4 (13.7)
BMI, mean (SD)	28.6 (5.0)
History of abdominal surgery, n (%)	314 (38.3)
VAS pain score, median (IQR)	8.0 (2.6)

Severity of pain and diversity of symptoms prior to surgery

The first column of Table 3 presents an overview of the prevalence of ROME-criteria for a biliary colic, characteristics of pain, and other abdominal symptoms at baseline. At baseline, 74.1% met the ROME-criteria for biliary colic. Pre-operatively, patients reported a variety of abdominal symptoms such as restricted eating (58.7%), abdominal fullness (55.0%), abdominal bloating (52.4%), not enjoying food (50.6%), flatulence (48.5%), abdominal noises (44.9%) and belching (39.1%) (Table 3).

Outcomes after cholecystectomy

Cholecystectomy was performed a median of five weeks after initial visit (IQR 6.0). Major surgical complications occurred in 2.4% and 1.9% of surgeries was converted from laparoscopic to open surgery. After surgery, 16.8% of patients had additional appointments at the outpatient clinic or presented at the emergency department. A heatmap illustrates an overview of the prevalence of ROME-criteria, characteristics of pain, and other abdominal symptoms at baseline and after six months follow-up (Table 3). Colors correspond with the reported prevalence. Pain persisted in 36.5% of patients. Prevalence of the three ROME-criteria was reduced to around 10% after LC (pain in attacks: 12.3%, pain located in upper right- or epigastric region: 10.3% and pain duration over 15-30 minutes: 8.3%, respectively), and 5.2% met all three criteria.

After follow-up, all abdominal symptoms were reduced significantly, except for diarrhea (17.2% vs. 16.7%, $P = 0.8$). The most frequently reported symptoms were: flatulence (24.6%), frequent bowel movements (19.1%), and restricted eating (18.4%).

Persistent vs. new-onset symptoms

Most symptoms were more likely to persist than to arise de novo. The most prevalent persisting symptoms were: flatulence (17.8%), restricted eating (14.5%) and not enjoying food (13.4%). Symptoms most likely to develop after LC were: frequent bowel movements (9.6%), bowel urgency (8.5%) and diarrhea (8.4%).

Patients with persisting pain

Supplementary Table 1 shows an overview of symptoms before and after LC and compares patients with and without persisting pain after LC. It illustrates that patients with persisting pain after LC more often had other abdominal symptoms at baseline as well as after follow-up. Moreover, patients with persisting pain more often met all three ROME-criteria (14.2%) and a third of patients indicated they still suffered from pain attacks (data not in Table).

Table 3. Prevalence of persistent and de novo symptoms after six months and cholecystectomy.

		Preoperative symptoms	Postoperative symptoms	Persistent	De novo
	Pain (%)	**100**	**36.5**	**36.5**	**0**
ROME-criteria	Pain in attacks (%)	85.4	12.3*	8.3	4.0
ROME-criteria	Pain location (%)	94.0	10.3*	10.3	0.3
ROME-criteria	Pain duration >15-30 min (%)	89.8	8.3*	7.7	0.6
ROME-criteria	Meet all 3 ROME-criteria† (%)	74.1	5.2*	3.8	1.4
ROME-criteria	Radiation to the back (%)	75.4	5.4*	4.3	1.1
ROME-criteria	No good effect of analgesics (%)	31.8	31.3*	25.0	6.3
Pain attacks	Pain attacks (%)	87.5	37.8	34.5	3.4
Pain attacks	Use of analgesics (%)	74.6	27.8	24.7	3.1
Pain attacks	Severe pain attacks (%)	95.4	37.3	36.3	1.0
Abdominal symptoms	Abdominal fullness (%)	55.0	13.2	10.1	3.0
Abdominal symptoms	Abdominal bloating (%)	52.4	14.8	11.7	3.0
Abdominal symptoms	Belching (%)	39.1	10.2	6.8	3.4
Abdominal symptoms	Flatulence (%)	48.5	24.6	17.8	6.8
Abdominal symptoms	Abdominal noises (%)	44.9	16.5	12.1	4.4
Abdominal symptoms	Frequent bowel movements (%)	26.2	19.1	9.5	9.6
Abdominal symptoms	Not enjoying food (%)	50.6	17.9	13.4	4.5
Abdominal symptoms	Restricted eating (%)	58.7	18.4	14.5	3.9
Abdominal symptoms	Regurgitation (%)	17.1	6.8	3.4	3.4
Abdominal symptoms	Nausea (%)	35.1	7.3	5.1	2.2
Abdominal symptoms	Diarrhea (%)	17.2	16.7	8.3	8.4
Abdominal symptoms	Bowel urgency (%)	21.7	16.6	8.0	8.5
Abdominal symptoms	Constipation (%)	16.3	7.6	4.1	3.4
Abdominal symptoms	Heartburn (%)	18.4	4.5	2.3	2.2

*Data available from the SUCCESS trial, n= 345

† Severe pain attacks, located in the upper right region, lasting for more than 15-30 minutes

Highest prevalence within group (column)

Lowest prevalence within group (column)

DISCUSSION

This study determines which symptoms are preoperatively present and are likely to persist after cholecystectomy and which may arise de novo. Although cholecystectomy effectively resolves typical biliary colic in most patients (95%), 36% of patients with uncomplicated symptomatic gallstone disease report persistent abdominal pain after LC. Symptoms like flatulence or restricted eating were most likely to persist after surgery. New-onset symptoms were frequent bowel movements (newly reported by 10% of patients), bowel urgency (newly reported by 9% of patients) and diarrhea (newly reported by 9% of patients). All symptoms were reduced significantly after 6 months of follow-up, except for diarrhea.

Comparison with other studies

In contrast with a systematic review from 2013, this study showed considerably less presence of symptoms after cholecystectomy. (6) Symptoms that persisted most often according to the review were: diarrhea (26-85%) and constipation (57-76%), while the most common de novo symptom was flatulence (0-62%). In this cohort, patients reported presence of these symptoms in 16.7% (diarrhea), 7.6% (constipation), 24.6% (flatulence), respectively. The wide ranges regarding the prevalence presented in the review can be explained by the use of many unvalidated questionnaires, small patient populations, large variations between included studies and low methodological quality.

Pathogenesis and etiology

LC resolves biliary colic, this is in line with a systematic review which previously reported a pooled relief rate for biliary pain of 92% (95% CI 86-96%). (15) A previous study of 200 patients found a significant reduction in regurgitation, heartburn, nausea, vomiting, bloating, disturbing abdominal gas and constipation, while the prevalence of diarrhea did not reduce significantly. (16) These findings are in accordance with the present study, in which diarrhea was the only symptom of which the presence did not significantly reduce. In our study, the most persistent symptoms were flatulence, not enjoying food, restricted eating. These persistent symptoms may be caused by coexisting gastrointestinal diseases like functional dyspepsia, irritable bowel syndrome or psychological stress. (5) The importance of coexisting gastrointestinal diseases is further endorsed by the fact that the prevalence of all abdominal symptoms was higher in patients with persisting pain (Supplementary Table 1), both prior and after LC. Furthermore, the present study showed that newly developed symptoms are diarrhea, bowel urgency and frequent bowel movements. These symptoms may be triggered by removal of the reservoir function of the gallbladder, causing a relative fat malabsorption in the early postoperative phase up to four weeks after LC. (5, 17) Up to 86% of patients with chronic diarrhea after cholecystectomy have test results suggestive of diarrhea due to bile acid malabsorption. (18) However, novel development of these symptoms occurred in less than 10% of patients (8.4% for diarrhea, 8.5% for bowel urgency and 9.6% for frequent bowel movements.

Guidance and challenges for clinical practice

The results of this study can be used in the future to better inform patients about outcomes of LC. Patients should be informed about the effectiveness of LC in taking away the typical biliary colic, but also about the risk that other abdominal pain or symptoms may persist or arise de novo after LC.

The detection of gallstones on ultrasound causes a clinical reflex in physicians (and

patients) to correlate these findings to a cause for the abdominal symptoms. Due to the high incidence of asymptomatic gallstones and high incidence of functional gastrointestinal symptoms in the general population, patients are at risk of being wrongly accused of having gallstone-related disease, because symptoms of functional gastrointestinal disorders often overlap with symptomatic gallstone disease. Moreover, patients with functional disorders are still stigmatized and patients (and physicians) prefer a 'clear-cut' diagnosis for which a 'straightforward' and 'easy to perform' treatment exists. (19, 20) In the presence of gallstones at baseline, it is often only after LC, when a biliary colic is made unlikely, that physicians and patients allow themselves to think of a functional gastrointestinal disorder.

Regarding the management of post cholecystectomy diarrhea, high-quality evidence is lacking. However, in recent years, the British Society of Gastroenterology and the Canadian Association of Gastroenterology (CAG) have suggested the 75-selenium homocholic acid taurine (SeHCAT) test to investigate bile acid diarrhea in patients with post cholecystectomy diarrhea. (21, 22). The SeHCAT test measures the extent of bile acid malabsorption. (23) After detecting bile acid malabsorption, treatment of bile acid diarrhea with a bile acid sequestrant like cholestyramine may resolve diarrhea in more than 70%. Unfortunately, cholestyramine is often poorly tolerated by patients and clear RCT-evidence is not available. (17, 18, 24)

Strengths and limitations

This study with prospective data comes with several strengths. Although a recent systematic review did not recommend a specific PROM to be used for patients undergoing cholecystectomy, only validated questionnaires were used and questionnaires were administered to patients preceding their outpatient clinic appointment. (25) Also, the use of multiple questionnaires in the same cohort at different points in time made it possible to distinct between different symptoms and etiologies. The study is limited based on the following aspects: only patients with complete follow-up at six months were included, which may lead to selection bias. Although our analysis did not show a difference between responders and non-responders in terms of gender and BMI, non-responders were younger and had more severe pain. However, the clinical significance of this VAS-difference is negligible. Lastly, symptom scores were converted into binary outcomes, resulting in loss of information, but facilitating the translation of the results to daily practice.

Future directions

Upper abdominal pain may be caused by gallstones, but could also by attributed to diseases like functional dyspepsia or irritable bowel syndrome. These conditions, however,

may have overlapping symptoms and affect similar patient populations. (26) This may lead to faulty diagnoses, ineffective interventions and worse outcomes. (27, 28) Currently, our research group is planning to perform a trial to investigate the potential of an individualized self-help guide for patients and a patient-tailored clinical decision support tool. This should support both the patient and the clinician and reduce diagnostic delay, time of uncertainty and the ineffective use of healthcare resources. Furthermore, 5-year follow-up of patients included in the SECURE-trial will reveal long-term residual complaints and received treatments or medication.

Conclusions

In conclusion, 36% of patients still report abdominal pain after cholecystectomy, but only 5% still meet all three ROME-criteria for a biliary colic. Symptoms like flatulence or restricted eating were most likely to persist after LC, whereas symptoms like frequent bowel movements, bowel urgency or diarrhea were most likely to develop de novo.

SUPPLEMENTARY TABLES

Supplementary table 1. Comparison between patients with persisting pain after cholecystectomy and pain-free patients, before and after cholecystectomy.

		Prior to cholecystectomy				After cholecystectomy			
		Total group (n=820)	Persistent pain (n=299)	Pain-free after LC (n=521)	P-value	Total group (n=820)	Persistent pain (n=299)	Pain-free after LC (n=521)	P-value
Abdominal symptoms	Abdominal fullness (%)	55.0	64.9	49.3	< .001	13.4	30.1	3.8	< .001
	Abdominal bloating (%)	52.4	60.1	48.0	< .001	15.2	31.4	6.0	< .001
	Belching (%)	39.1	44.3	36.1	0.02	10.4	17.1	6.5	< .001
	Flatulence (%)	48.5	57.4	43.3	< .001	24.9	37.8	17.5	< .001
	Abdominal noises (%)	44.9	53.4	40.0	< .001	16.6	32.1	7.7	< .001
	Frequent bowel movements (%)	26.2	33.8	21.8	< .001	19.3	32.4	11.7	< .001
	Not enjoying food (%)	50.6	60.5	44.8	< .001	18.3	29.8	11.7	< .001
	Restricted eating (%)	58.7	66.6	54.2	0.001	18.7	35.1	9.2	< .001
	Regurgitation (%)	17.1	22.0	14.2	0.005	6.8	13.4	3.1	< .001
	Nausea (%)	35.1	44.3	29.8	< .001	7.3	13.0	4.0	< .001
	Diarrhea (%)	17.2	22.4	14.2	0.003	17.0	25.8	11.9	< .001
	Bowel urgency (%)	21.7	27.8	18.1	0.001	16.7	27.8	10.4	< .001
	Constipation (%)	16.3	20.7	13.8	0.01	7.9	14.4	4.2	< .001
	Heartburn (%)	18.4	24.0	15.2	0.002	4.5	8.7	2.1	< .001

LC: Laparoscopic cholecystectomy, GIQLI: GastroIntestinal Quality of Life Index,

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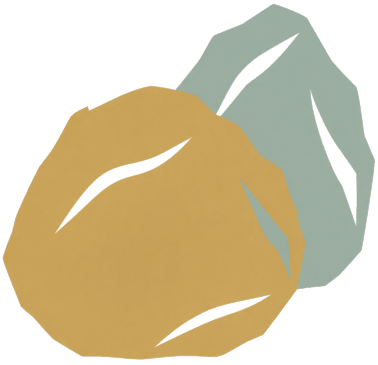
PART II

Revisiting the Assessment of Outcomes in Gallstone Disease





CHAPTER

6

A mixed-methods study to define Textbook Outcome for the treatment of patients with uncomplicated symptomatic gallstone disease with hospital variation analyses in Dutch trial data

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HPB 2023

ABSTRACT

BACKGROUND International consensus on the ideal outcome for the treatment of uncomplicated symptomatic gallstone disease is absent. This mixed-method study defined a Textbook Outcome (TO) for this large group of patients.

METHODS First, expert meetings were organised with stakeholders to design the survey and identify possible outcomes. To reach a consensus, results from expert meetings were converted in a survey for clinicians and one for patients. During the final expert meeting, clinicians and patients discussed survey outcomes and a definitive TO was formulated. Subsequently, TO-rate and hospital variation were analysed in Dutch hospital data from patients with uncomplicated gallstone disease.

RESULTS First expert meetings returned 32 outcomes. Outcomes were distributed in a survey among 830 clinicians from 81 countries and 645 Dutch patients. Consensus-based TO was defined as no more biliary colic, no biliary and surgical complications, and the absence or reduction of abdominal pain. Analysis of individual patient data showed that TO was achieved in 64.2%(1002/1561). Adjusted-TO rates showed modest variation between hospitals(56.6-74.9%).

CONCLUSION TO for treatment of uncomplicated gallstone disease was defined as no more biliary colic, no biliary and surgical complications, and absence or reduction of abdominal pain.TO may optimise consistent outcome reporting in care and guidelines for treating uncomplicated symptomatic gallstone disease.

INTRODUCTION

Approximately, 5-25% of the Western population has gallstones. (1) The majority of patients with gallstones remain asymptomatic. (2, 3) Only 20% of patients will develop typical episodes of a biliary colic, defined by the ROME III criteria. (4) Current international guidelines advise laparoscopic cholecystectomy (LC) to treat persistent symptomatic gallstone disease, while non-operative management is appropriate in patients with a single or infrequent biliary colic. (5, 6) LC for uncomplicated gallstone disease is a safe procedure with an associated risk of severe complications (i.e. bile duct injury) of less than 2%. (7) However, up to 40% of patients suffer from persistent abdominal pain one year after LC, possibly due to imprecise patient selection for surgery. (8) Persistent symptoms compromise the affecting quality of life, and put a considerable burden on healthcare systems' expenses. (9)

Quality and outcome assessment is important in high volume surgical procedures. (10, 11) However, the outcomes of treatment are commonly expressed as single indicators such as morbidity, mortality or readmission-rates, while patient-reported outcomes are less likely to be incorporated. (12) A composite endpoint that includes all relevant outcomes offers a better reflection of overall quality of treatment. Textbook outcome (TO) is an emerging composite outcome that includes all relevant treatment results that reflect a desirable treatment outcome. (13) A TO has been defined for several surgical procedures, but rarely for the management of gastrointestinal diseases such as gallstones. (14-16) International consensus on the definition of a specific TO for uncomplicated gallstone disease facilitates comparing relevant treatment outcomes between hospitals and in research.

The main objective of this mixed method study was to define TO for treatment of patients with uncomplicated gallstone disease, based on consensus in expert meetings and an international survey. Secondly, this study determines the TO-rate and the variation in TO-rate between hospitals in the Netherlands on basis of available prospectively generated patient data.

METHODS

Study design

This study has a mixed methods approach, combining qualitative and quantitative methods to define a consensus-based definition of TO for treatment of patients with uncomplicated gallstone disease. As treatment may be managed through surgery (LC) or conservatively, the TO encompasses both treatment options. A flowchart of the steps of the study is shown in Figure 1. First, two expert meetings were organized to identify all

possible outcomes of treatment in patients with uncomplicated symptomatic gallstone disease. Only health related outcomes (e.g. pain reduction, complications, treatment satisfaction) were included. These outcomes were used for the design of the surveys. Subsequently, two surveys were developed to assess which of the outcomes were considered ideal outcomes: one survey for gastroenterologists and surgeons, which was distributed internationally and one survey for Dutch patients with a history of gallstone disease. Third, during a final expert meeting, the results from the survey were discussed by clinicians and patients to reach consensus on the definition of TO. In this step the final definition of TO was established. For the secondary aim, we benchmarked the established definition of TO using data from two Dutch multicentre trials, and compared the rate of TO between participating hospitals (step 4, Figure 1). We followed the Standards for Quality Improvement Reporting Excellence (SQUIRE) guideline. (17) Patients and public were involved in the expert meeting and dissemination of the survey of the survey.

Final definition of Textbook Outcome

The primary endpoint is a consensus-based definition of TO for treatment of patients with uncomplicated gallstone disease. An agreement rate of >80% per surveyed outcome was considered as consensus and resulted in the item being included in the definition of TO. (18)

Expert meetings

In a first round, two expert meetings were organized (October 2021). The participants were nine gastrointestinal surgeons, two gastroenterologists, one methodologist (FA), and two patients with a history of symptomatic gallstone disease. The aim of these expert meetings was to list all possible outcomes for the design of the survey on operative and non-operative treatment for uncomplicated symptomatic gallstone disease. Participants were asked to think of both positive and negative outcomes, with or without undergoing surgery.

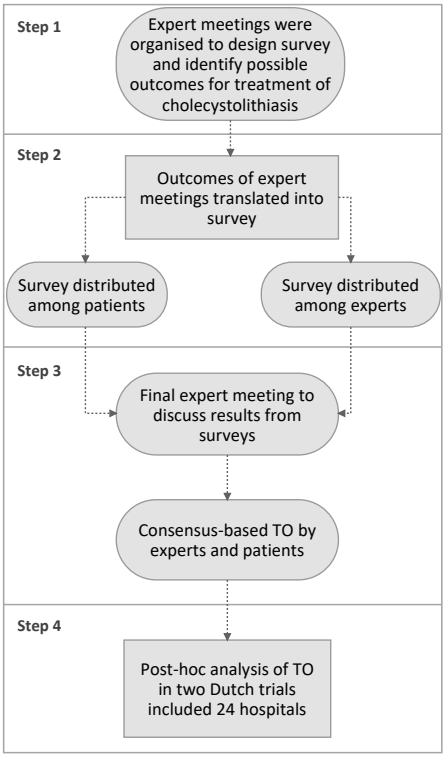

Figure 1. Flowchart of study steps. This mixed method included four steps: Step 1: Expert meetings with experts and patients with history of gallstone disease, Step 2: (Inter)national survey among experts and patients, Step 3: Final expert meeting to discuss results from surveys and consensus-based TO by experts and patients, Step 4: Assessment of the TO-rate in Dutch trial data.

Survey among clinicians

To determine ideal outcomes for the definition of TO, an international survey with all possible outcomes from the first expert meetings was distributed among clinicians. The survey included 22 questions about possibly important outcomes after treatment such as abdominal pain and symptoms, satisfaction, complications (biliary and surgical), and de novo complaints after treatment (survey in Appendix I). Questions were scored on a 5-point Likert scale, ranging from strongly disagree to strongly agree. Additional questions on the respondents' occupation (surgeon or gastroenterologist), and resident in training or not in training were also part of the survey.

To disseminate the survey, we approached an international group of collaborating experts in the field of gastrointestinal surgery and gastroenterology. These experts were asked to disseminate the survey among colleagues through multiple channels including social

media. We identified experts through a systematic literature search and contacted corresponding authors of studies on outcomes of LC published in the last 10 years. Dutch collaborating experts of the study group were local investigators of two prospective trials. The Dutch Society for Gastrointestinal Surgery (NVGIC), the Dutch Society for Gastroenterology (NVGE), the Association of Upper Gastrointestinal Surgery of Great Britain and Ireland (AUGIS), and the International Hepato-Pancreato-Biliary Association (IHPBA) distributed the survey among their members via direct e-mail and online. Additionally, the survey was distributed via social media including WhatsApp, Twitter, LinkedIn. As confirmation of expertise, surgeons were subsequently asked if the "critical view of safety" could be identified on a photo, and gastroenterologists were asked if the pylorus was visible on a photo taken during an upper gastrointestinal tract endoscopy. The survey was open between December 2021 and March 2022. Incomplete survey responses and responses with incorrect answers on confirmation of expertise were excluded from the analysis.

Survey among patients

In addition, to determine ideal outcomes for the definition of TO according to patients, a survey was conducted among patients with abdominal symptoms and gallstones who participated in recent multicentre Dutch trials (SECURE-trial, NTR4022), SUCCESS-trial (NTR7069), and PERFECT-trial (NTR7307)). (8, 19, 20) Patients who provided written consent to be contacted for future research were contacted by e-mail. The patient survey was based on the outcomes of the expert meetings and comprised 18 questions (survey in Appendix II). The questions were about possibly important treatment outcomes such as abdominal pain and symptoms, and complications (biliary and surgical complications). The survey was written in plain language and checked for easy reading Questions were scored on a 5-point Likert scale, ranging from strongly disagree to strongly agree. The survey was open between January 2022 and March 2022. Incomplete survey responses were excluded from analysis.

Consensus meeting and determination of TO-rates

In a final round (September 2022), two expert meetings were organized, and the same experts as the first round of expert meetings were involved. The aim of this final expert meeting was to reach consensus between clinicians and patients on the definition of the TO. The outcomes of both surveys among clinicians and patients were compared and discussed. Based on the agreement rate (consensus rate of >80% per surveys), items were selected and a TO was formulated. Final definition of a TO was defined during this last meeting.

Previous Dutch trials

Assessment of the TO-rate in real data was performed for all patients included in the SECURE and SUCCESS-trial. (8, 19) In these studies, all patients aged 18-95 years old, referred to a surgical outpatient clinic for abdominal pain with ultrasound proven gallstone disease and/or sludge were eligible for inclusion. For the SECURE-trial, patients were included in 24 hospitals between February 2014 and April 2017. For the SUCCESS-trial, patients were included in 7 hospitals between October 2017 and June 2019. Six hospitals participated in both studies at different moments. In total, 1067 patients were included in the SECURE-trial and 494 patients in the SUCCESS-trial. (8, 19)

In both studies, included patients received questionnaires after the first outpatient clinic visit (baseline) and at 6 months of follow-up. Patient characteristics (age, sex, BMI, history of abdominal surgery, smoking and use of alcohol) were registered at baseline. The study questionnaires consisted of the Izbicki Pain Score (IPS) and questions on abdominal symptoms. (21) The IPS consists of four questions regarding frequency of pain, use of pain medication, disease-related inability to work and intensity of pain based on a Visual Analog Scale (VAS-score, 0 = no pain and 10 = worst imaginable pain). After six months of follow-up, individual patients' medical records were examined for recurrence of biliary colic with hospitalization, biliary complications, and surgical complications. Surgical complications were classified in accordance with the Clavien-Dindo classification. Bile duct injuries were classified as minor or major. (22) (23)

Statistical analyses

To describe the trial data, categorical variables were reported as counts with percentages and continuous variables as median values with corresponding Interquartile Ranges (IQR). Absence of pain was defined as a VAS ≤ 4 and clinically relevant pain reduction as a reduction of at least 4 points on the VAS pain score after 6 months (baseline VAS pain score minus 6-month VAS pain score, ΔVAS>4). TO was achieved if a patient met all selected criteria for a TO at six months of follow-up (Box 1). (13)

Hospital variation in TO-rates were analysed. To avoid small sample variation, hospitals with less than 30 included patients were excluded from these analyses. TO-rates per hospital were adjusted for patient characteristics (case-mix adjusted (standardized) TO-rate per hospital). The calculation of the case-mix-adjusted TO per 100 gallstone patients consisted of 3 steps: first, crude TO-percentages were calculated (observed rates). Second, a logistic regression with TO as outcome and age, sex, and BMI >25 kg/m^2 as covariates was performed to assess the expected TO-rate per hospital; third, the observed TO-rate per 100 patients was divided by the expected TO-rate per 100 patients and multiplied by the national average of TO.

To express the amount of variation, histograms were drafted and the factor difference between high and low hospitals was calculated. Subsequently, the mean of the case-mix-adjusted TO-rates of the three highest hospitals was divided by the mean of the case-mix-adjusted TO-rates of the three lowest hospitals. We consider a factor score of more than 2.0 as a modest and relevant variation. Factor scores were calculated between hospitals. A funnel plot was constructed to detect outliers and to distinguish systematic variation from random variation. Data analysis was performed using SPSS, version 27.0 (IBM) and R version 4.1.3.

RESULTS

Outcomes of expert meetings

In total, fifteen different experts (surgeons, gastroenterologists, methodologist and patients with a history of gallstone disease) participated in two expert meetings (Table 1, Step 1). Expert meetings resulted in 32 different important clinical outcomes for treatment of uncomplicated gallstone disease. The 32 different outcomes were subdivided into eleven subgroups (Table 1, Step 2). The eleven outcome subgroups included biliary complications, surgical complications, morbidity and mortality, abdominal pain and symptoms, satisfaction, daily activities, food intolerance, de novo symptoms, referral, new diagnostics, treatment and treatment costs. Outcomes of expert meetings were translated into surveys and disseminated among clinicians and patients. An overview of the first expert meetings and survey responses is shown in Table 1.

Survey for clinicians

Between December 2021 and March 2022, 830 clinicians responded to the survey. The survey was completed by 603 clinicians (72.6%) from 81 countries. Three percent of the responders (n=26) incorrectly answered the question to test their expertise and were excluded from the analysis. An agreement rate of >80% per surveyed item was achieved in five outcomes: no recurrent biliary colic with hospitalization (90% agreement rate), absence of abdominal pain after treatment (88%), no surgical complications (86%), patient is satisfied (85%), no biliary complications (81%).

Survey for patients

Between January 2022 and March 2022, 1653 patients received a digital invitation for the survey, of whom 645 opened the survey. The survey was completed by 490 patients (75.9%). An agreement rate of >80% per surveyed item was achieved in eight outcomes: no recurrent biliary colic with hospitalization (94%), impairment of daily activities (93%),

good physical health (89%), good night's sleep (87%), absence of food intolerance (86%), absence of abdominal pain after treatment (84%), no biliary complications (83%), pain reduction after treatment (82%).

Table 1. Participants and outcomes of expert meeting sessions and international survey participants

Step 1. Expert meeting sessions participants[1]

Participants	Total	Session 1	Session 2
Gastrointestinal surgeon, n	9	5	4
Gastroenterologist, n	2	1	1
Methodologist, n	1	1	1
Patient with history of gallstone disease, n	2	1	1

Step 2. Complications and outcomes reported in expert meetings and subsequently included in the survey [2]

Biliary related	Cholecystitis Biliary pancreatitis Choledocholithiasis Cholangitis Icterus Post-ERCP complication Mirizzi-syndrome
Surgery related	Surgical related complications like wound infection Bile duct injury and bile leakage Bile duct stenosis
Morbidity and Mortality	Hospital admission ICU admission Deceased
Abdominal pain and symptoms	Absence or reduction of abdominal pain Absence of biliary colic No recurrent biliary colic with hospitalization No improvement of abdominal pain after cholecystectomy Spontaneous recovery of abdominal pain without treatment
Satisfaction	Satisfied patient after treatment
Daily activities	Hindrance due to abdominal complaints during daily activities (i.e., work, sleep, and hobbies)

Food intolerance	Normal food habits pre and post cholecystectomy Diet with or without biliary colic
De novo symptoms	No bloating No diarrhoea Normal defecation No weight-gain
Referral	No new referral for persistent abdominal complaints
New diagnostic and treatment	Upper GI-endoscopy tract endoscopy ERCP
Treatment costs	No extra healthcare costs Reduction of healthcare costs

Step 3. Response of (inter)national survey

	Clinicians	Patients
Total respondents, n	830	645
Completed, n (%)	603 (72.6)	490 (75.9)
Countries	81	1
Age, median (IQR)	43.0 (36.0-53.0)	56.0 (45.0-64.0)
Surgeons/Gastroenterologists, n (%)	781 (94)/ 49 (6)	

Abbreviations: Endoscopic Retrograde Cholangiopancreatography (ERCP), Intensive care unit (ICU), Gastrointestinal (GI), Interquartile range (IQR)

Table 2. Agreement rate of items from surveys in which consensus was reached in clinicians and patients with a history of uncomplicated gallstone disease
An agreement rate of 80% per item was considered as consensus.
* Outcome item was selected as criteria for composite TO.

Reported outcome	Agreement rate among 603 clinicians	Reported outcome	Agreement rate among 490 patients
No recurrent biliary colic with hospitalization*	90%	No recurrent biliary colic with hospitalization*	94%
Absence of abdominal pain*	88%	No hindrance in daily activities	93%
No surgical complications*	86%	Good physical health	89%
Patient is satisfied	85%	Good night's sleep	87%
No biliary complications*	81%	Absence of food intolerance	86%
		Absence of abdominal pain*	84%
		No biliary complications*	83%
		Pain reduction*	82%

Consensus-based TO

In a final expert meeting, a consensus based TO was established based on outcomes of the surveys. Outcomes considered to be not directly affected by treatment for symptomatic gallstone disease (such as good physical health) were discarded after discussion with participating patients. The definitive TO for treatment of patients with uncomplicated gallstone disease was defined as follows: no recurrent biliary colic with hospitalization, absence or relief of abdominal pain after treatment, absence of biliary complications (i.e., acute cholecystitis, biliary pancreatitis, choledocholithiasis and cholangitis), and absence of surgical complications (i.e. bile duct injury and bile leakage) regardless the duration of follow-up. The consensus based TO is shown in Box 1.

Box 1. Textbook outcome for treatment of patients with uncomplicated gallstone disease

Composite Textbook Outcome for treatment of uncomplicated gallstone disease:

No recurrent biliary colic with hospitalization

and

Absence or reduction of abdominal pain

and

Absence of biliary complications

and

Absence of surgical complications

TO-rate and hospital variation

Hospital variation in TO-rates were analysed in the trial data of two Dutch trials. (8, 19) Overall, TO was achieved in 64.2% of patients (1002/1561). Patients who underwent LC reached TO more often compared to patients with conservative treatment (76.1% vs. 64.1%, $P < .001$).

The main cause of not reaching a TO was persistent abdominal pain, reported by 365 of the 1561 patients (23.4%). A biliary complication occurred in 108 patients (6.9%); recurrent biliary colic resulting in hospital admission in 47 patients (3.0%), other biliary complications (i.e. cholecystitis, biliary pancreatitis) in 61 patients (3.9%). A surgical complication occurred in 13.7% of patients (154/1124); bile duct injury in 1.1% of patients (12/1124), of which four were major bile duct injury (0.4%). The overall rate of TO and the contribution of individual criteria in reaching a TO are shown in Figure 2 and Supplementary Table S1 and Supplementary Table S2.

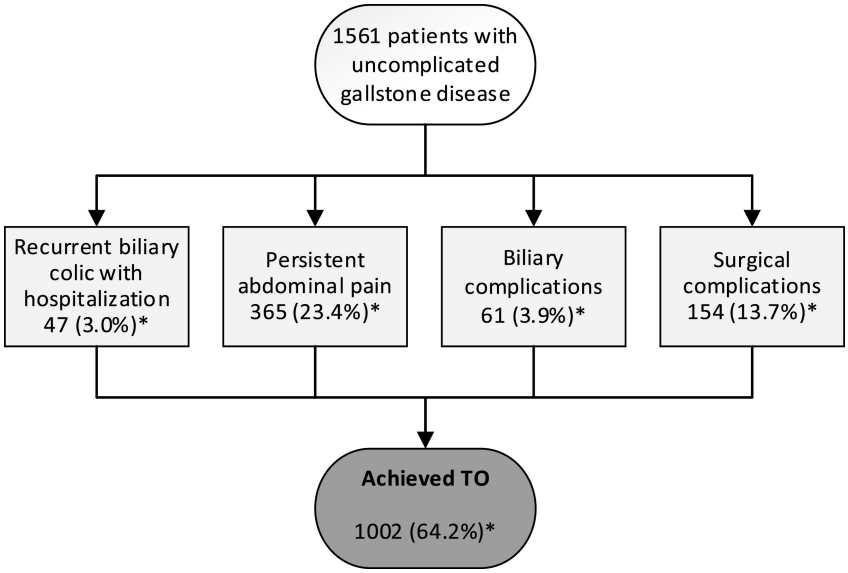

Figure 2. Contribution of selected criteria in achieving Textbook Outcome * Textbook Outcome (TO) for treatment of patients was defined as no recurrent of biliary colic with hospitalization, absence or reduction of abdominal pain, absence of biliary complications, and absence of surgical complications. TO was determined in 1561 patients from 24 hospitals

Eight of the 24 participating hospitals were excluded because of less than 30 included patients, leaving 1432 patients from 16 hospitals for the variation analyses (91.7%, 1432/1561). There were 14 general hospitals and two academic hospitals. TO was achieved in 63.8% of patients (914/1432) in 16 hospitals and thus comparable with the proportion of TO (64.2%) in the total population of 24 hospitals. The histogram (Figure 2) with unadjusted TO-rates shows modest variation between hospitals, ranging from 56.6%-75.6%. Standardized TO-rates ranged from 56.6%-74.9%. The calculated factor score was 1.26. The funnel plot (Figure 3) shows there were no systematic outliers.

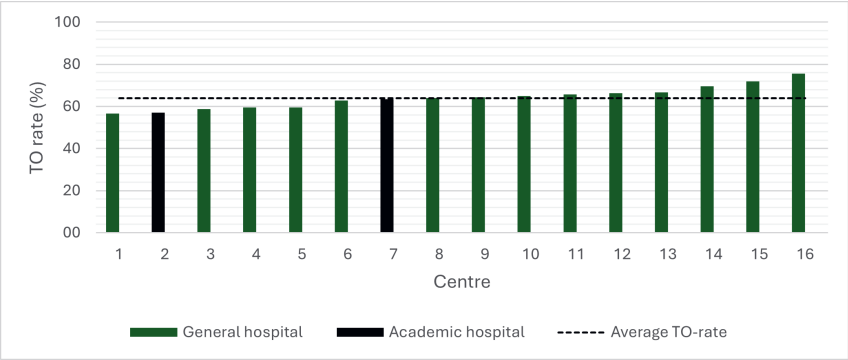

Figure 3. Histogram with unadjusted TO-rates between hospitals Eight of the 24 participating hospitals were excluded because of less than 30 included patients, leaving 1432 patients from 16 hospitals for the variation analyses. Average TO-rate was 63.8% (914/1432). Unadjusted TO-rate ranging from 56.6%-75.6%

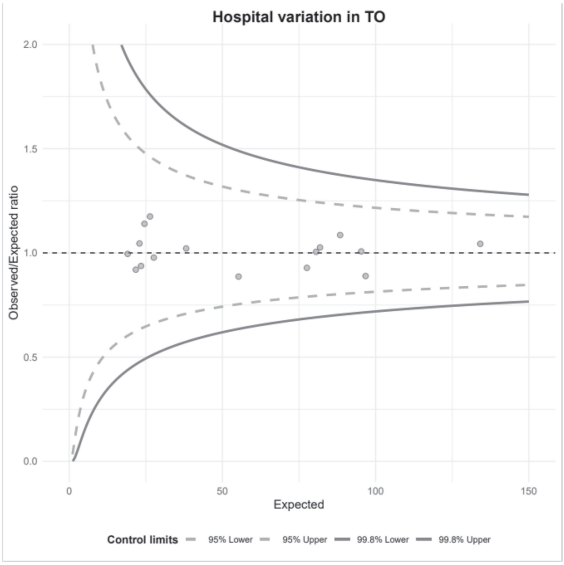

Figure 4. Funnel plot of between-hospital variation in Textbook Outcome after treatment for gallstone disease during 2014-2019
*Observed/Expected ratio: observed number of Textbook Outcome patients divided by expected number of Textbook Outcome patients.
** Expected number of patients achieving TO, based on population characteristics (age, BMI and gender)

DISCUSSION

This study reports an international consensus-based definition of TO for the treatment of patients with uncomplicated gallstone disease. TO in these patients was defined as no recurrent biliary colic with hospitalization, absence or reduction of abdominal pain, absence of biliary complications and absence of surgical complications. Post-hoc analysis of Dutch trial data showed that 64% of patients treated for uncomplicated gallstone disease reached a TO with modest outcome variation between hospitals and without any true outliers.

The multidimensional indicator TO is a novel but emerging measure for the quality of medical treatment outcomes. (14, 15) Surgical treatments with high impact have been evaluated based on the TO strategy. In relation to the TO defined in the present study, experiences of clinicians, as well as patients, were considered. TO for patients with gallstones is a composite measure of patient-reported outcomes and biliary and surgical complications. The reported complication rates in the analysed patient series are low and consistent with the literature. (1, 24) Although surgery is associated with a higher TO rate than conservative management (76.1% vs. 64.1%, $P < .001$), improved patient selection for surgery remains critical as the most modifiable factor contributing TO is the reduction of persisting abdominal pain after cholecystectomy. Persisting pain may be explained by the fact that 30% of patients with gallstone disease fulfil the criteria for FGID (i.e. functional dyspepsia and irritable bowel syndrome) and underlying FGID negatively impact the outcome of cholecystectomy. (20) Moreover, the indication for cholecystectomy for uncomplicated gallstone disease varies among clinicians and guidelines. (25) There is no (international) consensus on the best criteria to select patients resulting in preference-sensitive care in cholecystectomy practices. (26) The selection of patients for cholecystectomy is challenging and the ROME III criteria fail to serve as diagnostic tool to deselect patients for cholecystectomy. (8) Recently, our study group developed a clinical decision tool to predict the probability of pain reduction after cholecystectomy. This validated model may aid surgeons and patients in deciding whether an operation will contribute to pain-relief and improve selection. A tool which may lead to higher TO-rates. (19)

A formal three-round Delphi survey recently led to a core outcome set for symptomatic gallstone disease. The developed set corroborates with the present outcome set that includes quality of life, patient satisfaction, postoperative pain, and surgical complications yet does not precisely define included outcomes. (27) A potential pitfall of a Delphi round is the selective recruitment and sustained participation of stakeholders. International dissemination via social media and a survey among patients may reflect values from more different stakeholders and perspectives from other national healthcare systems. The added value of the present TO is a specific definition of outcomes and val-

idation in a large group of international clinicians and patients. Compared to the core outcome set, the current TO is applied in clinical data, illustrating the potential application to optimize consistent outcome reporting in care, clinical trials and guidelines for patients with symptomatic gallstones. A recent retrospective analysis from the UK assessed a different TO definition for LC in 2166 patients and reported a TO rate of 85%. (28) TO was defined as an unremarkable surgical procedure without post-operative complications, leaving out patient-reported outcomes. Our expert meeting agreed that a surgically focused definition shows insufficient equality of the most important stakeholder, the patient.

This study has strengths and limitations. To define TO, comprehensive methods were used in which both clinicians and patients were involved. The composed surveys were distributed by colleagues, and national and international associations. The established collaborative group was able to reach clinicians from 81 countries from all continents, which provides a support base for future implementation of this TO in clinical practice. In addition, an assessment of TO in Dutch trial data was performed to provide valuable insight into the impact of specific factors in reaching a TO. This study has several limitations. For instance, no formal Delphi method was performed to reach consensus. This was considered but not achieved during the initiation phase of the project due to practical considerations. Regardless, the adopted method provided possibilities for regular feedback during different stages of the study (i.e. during expert meetings, within the survey and during the final consensus meetings). Furthermore, patient reported outcome measures may not always be suitable for a TO as not all outcomes relevant to patients were included in the definitive TO. For example, 87% of patients indicated that a good night's sleep should be in the TO. During the final expert meetings, outcomes such as sleep were discussed, and it was determined that they were too non-specific for gallstone disease and depended on too many other factors. Cardiopulmonary complications are relevant outcomes for elderly patients, but this was not separately reported. Although patients with uncomplicated gallstone disease in the present series are relatively young (mean age 50) and healthy (85% ASA I), cardiopulmonary complications are more prevalent in an older population, more prone to complicated gallstone diseases such as cholecystitis and choledocholithiasis. Finally, neither the expert meeting members nor the experts defined a time period within which TO should be achieved. In the present analysis TO rate was assessed at six months follow-up, but the need for longer follow-up is for discussion.

The reported between-hospital variation in TO-rate shows that measuring TO for patients with gallstones is a feasible, transparent and is an informative way to assess quality assurance. The present international collaboration and global survey to define TO for patients with gallstones may serve as a basis for an international benchmark in future

gastrointestinal care. This benchmark addresses the need to include patient-reported outcomes in quality assessments. Implementation of TO in local services will not primarily drive clinicians to reduce biliary and surgical complications but mainly to better select patients for cholecystectomy and reduce the number of patients with postoperative abdominal pain.

In conclusion, TO for treatment of patients with symptomatic gallstones is defined with input from patients, surgeons and gastroenterologists. Variation between hospitals in TO-rate is modest, and failure to achieve a TO in gallstone patients is primarily due to persistent abdominal pain. These findings both illustrate the need to better select patients for either conservative or operative treatment.

SUPPLEMENTARY TABLES

Supplementary Table S1. Baseline characteristics of patients included for Textbook Outcome (TO) analysis in Dutch trial data.

	Total (N=1561)	**TO (N=1002)**	**No TO (N=559)**	**P**
Sex, female n (%)	1143 (73.2)	728 (72.7)	415 (74.2)	0.498
Age, median (IQR)	50 (38.0-60.0)	50.0 (39.0-60.0)	49.0 (38.0-60.0)	0.143
BMI, median (IQR)	27.5 (24.7-31.4)	27.4 (24.6-31.2)	28.0 (24.8-31.9)	0.074
History of abdominal surgery, yes (%)	590 (37.8)	363 (36.2)	227 (40.6)	0.087
Biliary colic[a], yes (%)	1046 (67.0)	699 (69.8)	347 (62.1)	0.002
Treatment at 6 months				
Laparoscopic cholecystectomy, yes (%)	1124 (72.0)	763 (76.1)	361 (64.6)	<.001

BMI missing for 1 patient (0.064%)

[a] Biliary colic in accordance with the ROME-criteria (severe pain attacks, located in the right upper quadrant or epigastrium, lasting for at least 15-30 minutes)

Supplementary Table S2. Patient outcomes of individual criteria of the Textbook Outcome (TO)

Selected criteria for TO	Total (N=1561)
No recurrent biliary colic with hospitalization, n (%)[b]	1514 (97.0)
Recurrent biliary colic with hospitalization, n (%)	47 (3.0)
Absence or reduction of abdominal pain, n (%)[a b]	1196 (76.6)
Persisting abdominal pain, n (%)	365 (23.4)
No biliary complications, n (%)[b]	1500 (96.1)
Biliary complication, n (%)	61 (3.9)
Cholecystitis, n (%)	21 (1.3)
Choledocholithiasis, n (%)	32 (2.0)
Cholangitis, n (%)	0
Biliary pancreatitis, n (%)	8 (0.5)
No surgical complication, n (%)[b]	970/1124 (86.3)
Surgical complication, n (%)	154 (13.7)
Bile duct injury [c]	
Minor injury, n (%)	8 (0.5)
Major injury, n (%)	4 (0.3)
Conservative therapy, n (%)	437 (27.9)
Composite Textbook Outcome rate, n (%)[b]	1002 (64.2)

[a] Absence or reduction of abdominal pain was defined as VAS ≤4 or reduction VAS pain score ≥4 points
[b] For the TO, the following criteria were selected: no recurrent of biliary colic with hospitalization, absence or reduction of abdominal pain at six months of follow-up, absence of biliary complications, and absence of surgical complications. TO was achieved in 1002 of 1561 patients.[c] Bile duct injury is classified in minor or major injury (23)

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CHAPTER

7

Unraveling factors associated with Textbook Outcome after cholecystectomy in patients with uncomplicated cholecystolithiasis: a post-hoc analysis of individual data of 1124 patients

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Surgery 2024



ABSTRACT

BACKGROUND A Textbook Outcome(TO) for management of uncomplicated cholecystolithiasis is the targeted clinical scenario and is characterized by no recurrent biliary colic, absence of surgical and biliary complications and absence or relief of abdominal pain. The aim of this study was to assess the incidence of TO after cholecystectomy and identify associated baseline factors.

METHODS Patients from two Dutch multicenter prospective trials between 2014 and 2019 (SECURE and SUCCESS trial) were included. The primary outcome was the proportion of patients with TO after cholecystectomy at six months follow-up. Regression analysis was used to identify which factors prior to surgery were associated with TO.

RESULTS A total of 1124 patients underwent cholecystectomy. TO at six months follow-up was reached in 67.9% of patients. Persistent abdominal pain was the main reason for failure to achieve TO. Patients who did achieve TO, more often reported severe pain attacks (89.4% vs 81.7%, p<.001) and/or biliary colic (78.6% vs 68.4%, p<.001) at baseline compared to patients without TO. Presence of biliary colic at baseline (OR=1.56, 95%-CI: 1.16-2.09, p=0.003), and nausea/vomiting at baseline (OR=1.33, 95%-CI: 1.01-1.74, p=0.039) were associated with TO. The use of non-opioid analgesics (OR=0.76, 95%-CI: 0.58-0.99, p=0.043) and pain frequency ≥1/month (OR=0.56, 95%-CI: 0.43-0.73, p<.001) were negatively associated with TO.

CONCLUSION TO is achieved in two-thirds of patients who undergo cholecystectomy for uncomplicated cholecystolithiasis. Intensity and frequency of pain, presence of biliary colic and nausea/vomiting at baseline are independently associated with achieving TO. A more stringent selection of patients may optimize the TO rate in patients with uncomplicated cholecystolithiasis.

INTRODUCTION

Laparoscopic cholecystectomy (LC) is the recommended treatment for patients with either symptomatic or complicated cholecystolithiasis (i.e. choledocholithiasis, cholecystitis, biliary pancreatitis). (1, 2) As such, LC is the most performed abdominal surgical procedure worldwide, accounting for over 700.000 operations in the USA each year. (3) Despite increasing awareness among surgeons that not all patients with abdominal pain and presence of gallstones will benefit from LC and improved patient selection, still one third of patients who underwent LC because of gallstones and abdominal pain report persistent pain. (4) Different randomized and nonrandomized trials investigated the optimal selection for cholecystectomy in patients with uncomplicated cholecystolithiasis. (4, 5)

First, several groups reported the uncertain outcome of LC. (4, 6, 7) Second, a prospective analysis of 401 gallstone patients found that 35% of patients also fulfilled the criteria for a functional gastrointestinal disorder (FGID), which hamper the outcomes after surgery. These poor outcomes were the rationale to develop a model to predict pain-relief after LC. (8, 9) The model included age, history of abdominal surgery, VAS pain score, positive response to simple analgesics, nausea during pain attacks and absence of heartburn. The factors highlights the importance of assessing patient characteristics, including FGID-related symptoms, preoperatively before deciding for LC in patients with abdominal pain and gallstones. Recently, a Textbook Outcome (TO) for the treatment of patients with uncomplicated cholecystolithiasis was defined in a mixed-methods study involving clinical experts from 81 countries and Dutch patients with a history of cholecystolithiasis. (10, 11) A Textbook Outcome (TO) is a composite outcome and includes all decisive parameters that define an ideal result instead of using single indicators, such as incidence of surgical complications or reintervention rates. (12, 13) TO was defined as: no recurrent biliary colic with hospitalization, absence of biliary- and surgical complications, and absence or reduction of upper abdominal pain (UAP) after treatment. (10, 11)

To make an informed decision for surgical treatment of uncomplicated cholecystolithiasis, it is valuable to acquire insights in factors associated with TO after cholecystectomy. In contrast with the previous randomized and nonrandomized trials, in which the focus was on persistent pain after surgery, this study is focused on the more comprehensive TO. The aim of this post-hoc study is to identify baseline factors associated with achieving TO six months after cholecystectomy in patients with uncomplicated cholecystolithiasis.

METHODS

Data Source and Study Population

For this post-hoc analysis, data were obtained from a Dutch randomized controlled trial (SECURE trial, METC 2013-129/NTR4022) and a Dutch prospective cohort (SUCCESS trial, METC 2017-3306/NTR7069). (4, 5) Both studies were approved by the medical ethical committees from the participating hospitals. In both trials, eligible patients were between 18-95 years-of-age with suspected of symptomatic uncomplicated cholecystolithiasis who were referred to a surgical outpatient clinic to discuss cholecystectomy. The current study included only consecutive patients who were treated by LC (Figure 1 Flowchart of included patients).

In both trials, patients filled out questionnaires at baseline and at six months' follow-up. The questionnaires assessed gastrointestinal symptoms (biliary colic in accordance with Rome III criteria and other abdominal symptoms including heartburn, difficult defaecation, bloating, nausea/vomitus and diarrhea), intensity of pain based on a Visual Analog Scale (VAS) score (0 = no pain and 10 = the worst imaginable pain), pain frequency and use of pain medication. The SECURE trial followed the Consolidation Standard of Reporting Trials (CONSORT), and the SUCCESS trial followed the Strengthening of the Reporting of Observational Studies in Epidemiology (STROBE). (14, 15)

Outcomes

The primary outcome of this study was the proportion of patients that reached TO following LC at six months follow-up. Secondary endpoints were differences between characteristics of patients with and without TO. (10) The following patient characteristics were assessed at baseline prior to surgery and were analysed to determine their association with TO: demographics (sex, age, body mass index [BMI]), pain characteristics (frequency of pain, use of simple anaesthetics, intensity of pain (Visual Analogue Scale (VAS) Pain score), and abdominal symptoms (nausea/vomiting, heartburn, abdominal bloating, diarrhea and difficult defecation). A logistic regression analysis was performed to identify associated factors to reach TO after LC.

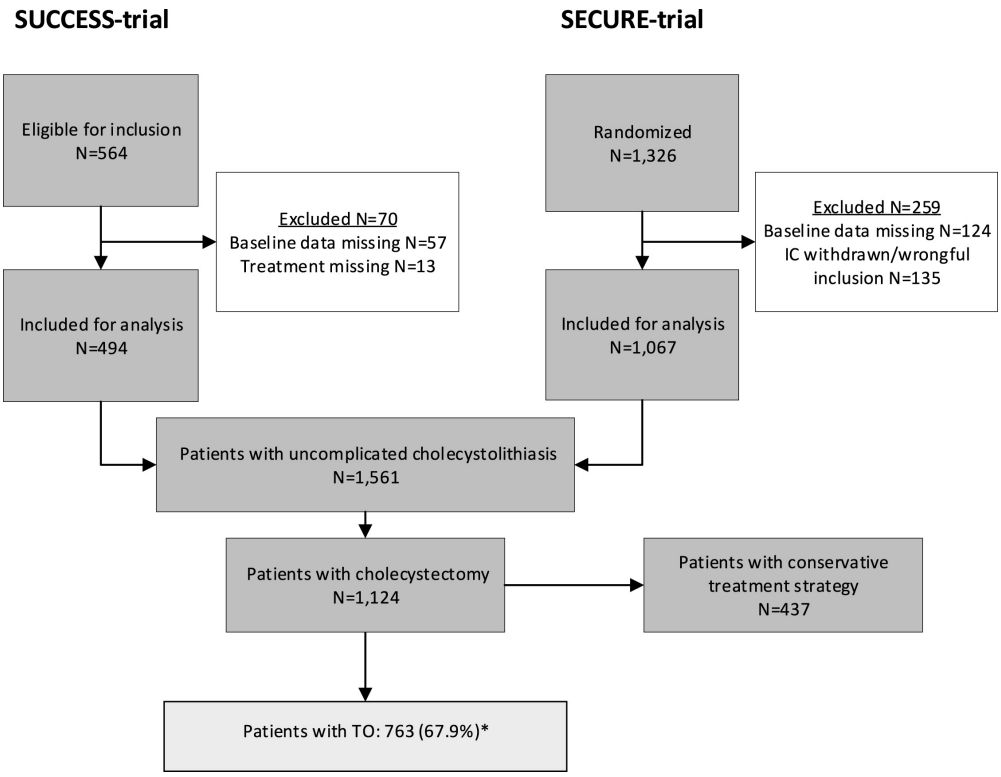

Figure 1. Flowchart of included patients

Data collection

Information on demographic characteristics were collected from the baseline survey. Clinical outcome data from all included patients were obtained after six months of follow-up. Medical records were evaluated for information on cholecystectomy (yes/no), recurrent biliary colic with hospitalization, biliary complications, and surgical complications. The following biliary complications were recorded and included: biliary pancreatitis, development of cholecystitis before cholecystectomy, choledocholithiasis, and cholangitis. The following surgical complications were recorded: wound infections, postoperative pain with prolonged hospital stay, bile spillage or bleed which led to drain placement and/or prolonged hospital stay, bile duct injury, Bile duct injuries were recorded and classified according to Bergman et al. (16)

Textbook Outcome

TO for treatment of uncomplicated symptomatic cholecystolithiasis was defined in an international mixed-method study. (10) TO was finally defined as no recurrent biliary colic with hospitalization, absence of biliary complications, absence of surgical complications and absence or reduction of upper abdominal pain. Hospitalization was defined as a visit at the emergency department with admission due to unresponsiveness to analgesics. Pain-free was defined as a VAS ≤ 4 and reduction of pain as a reduction of ≥4 points on the VAS pain score. (10) Achieving a 4-point decrease on an 11-point VAS scale represents more than the minimum 30% pain relief required by regulatory bodies such as the US Food and Drug Administration or the European Medicines Agency for pain medications. (17)

Statistical analysis

We used TO after six months follow-up as a dichotomous outcome variable. (4, 5) TO was achieved when patients met all selected criteria for TO at six months follow-up. (18) Baseline characteristics (age, BMI) and information from the survey (pain scores) were presented as mean (SD) or median (IQR) depending on distribution. Dichotomous variables were summarized by frequencies and proportions (pain characteristics, fulfilment of the Rome-III criteria and abdominal symptoms). Differences between patients with and without TO were analysed using chi-squared tests, Fisher's exact tests, independent t-tests, or Mann-Whitney-U tests, depending on the type of data.

Variables associated with achieving TO were assessed using univariable and multivariable logistic regression analysis. TO state served as the dependent binary variable in this analysis. In order to ensure sufficient power, a minimum of 10 outcome events per selected predictor variable was applied as a rule of thumb. (19) Continuous variables were tested for linear assumption by adding quadric and tertiary terms. Collinearity of the individual variables was tested and no correlation between individual variables was found. A multivariable logistic regression with Wald backward elimination was performed to explore which factors were associated with TO. *P* values of less than 0.05 were considered statistically significant and odds ratios (OR) and their 95% confidence intervals (CI) were reported. Data analysis was performed using IBM SPSS, version 27 (SPSS Inc. Chicago, IL USA).

RESULTS

Patients and characteristics

Patients were included between 2014 and 2017 in the SECURE trial (N=1067) and between October 2017 and June 2019 in the SUCCESS trial (N=494). A total of 1124 patients underwent LC (N=729 in the SECURE trial; N=395 in the SUCCESS trial) and were included for analysis (Figure 1).

Table 1 shows an overview of patient characteristics. Seventy-five percent (848/1124) of the patients are female, with a mean age of 48.0 years (SD 20) at study baseline and median BMI of 27.7 kg/m^2 (IQR 24.7-31.6). Biliary colic was reported in 75.4% of patients (n=847 out of 1124). Median VAS pain score at baseline was 8.0 (IQR 6.5-9.0).

Table 1. Baseline characteristics and a comparison of patients with and without TO after cholecystectomy

	Total N=1124	Patients with TO N=763 (67.9%)	Patients without TO N=361 (32.1%)	P
Baseline characteristics				
Age, mean (SD)	48.0 (20)	48.0 (20)	48.0 (14)	0.884[%]
Sex, Female n (%)	848 (75.4)	576 (75.5)	272 (75.3)	0.958[&]
BMI, median (IQR)	27.7 (24.7-31.6)	27.5 (24.7-31.2)	28.3 (24.8-32.1)	0.125[%]
Abdominal surgery in history, n (%)	426 (37.9)	278 (36.4)	148 (41.0)	0.141[&]
Baseline – Abdominal pain				
VAS pain score, median (IQR)	8.0 (6.5-9.0)	8.0 (6.6-9.0)	8.0 (6.4-9.0)	0.044[%]
Pain frequency >1/month, n (%)	444 (42.0)	264 (37.1)	180 (52.0)	.001[&]
Baseline – Biliary symptoms				
Severe pain in attacks (%)[1]	977 (86.9)	682 (89.4)	295 (81.7)	.001[&]
Located in right upper quadrant or epigastric region (%)[2]	1059 (94.2)	721 (94.5)	338 (93.6)	0.561[&]
Duration of pain longer than 15-30 min (%)[3]	1002 (89.1)	695 (91.1)	307 (85.0)	0.002[&]
Biliary colic by ROME III-criteria[a], n (%)	847 (75.4)	600 (78.6)	247 (68.4)	.001[&]
Pain radiating to the back, n (%)	852 (75.8)	572 (75.0)	280 (77.6)	0.343[&]
Use of non-opioid analgesics, n (%)	656 (58.4)	430 (56.4)	226 (62.6)	0.047[&]
Urge to move during pain attack, n (%)	871 (77.6)	602 (79.0)	269 (74.5)	0.092[&]
Baseline – Functional symptoms				
Nausea/vomiting, n (%)	630 (56.0)	445 (58.3)	185 (51.2)	0.026[&]
Heartburn, n (%)	276 (24.6)	182 (23.9)	94 (26.0)	0.427[&]
Abdominal bloating, n (%)	510 (45.4)	348 (45.6)	162 (44.9)	0.379[&]
Diarrhea, n (%)	184 (16.4)	130 (17.0)	54 (15.0)	0.817[&]
Difficult defecation, n (%)	200 (17.8)	129 (16.9)	71 (19.7)	0.258[&]

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); IQR, interquartile range; VAS, visual analog scale. [a] All three ROME criteria: 1,2,3

Textbook outcome after cholecystectomy

At six months follow-up, TO was achieved by 763 of 1124 patients (67.9%). As shown in Table 2, main reason for not achieving TO (32.1%, n=361) was persistent upper abdominal pain (15.4%, n=173). Other reasons for failing TO included surgical complications (13.7%, n=154), of whom 12 patients were treated for bile duct injury with four patients with a major bile duct injury (0.4%). Other surgical complications were wound infections (n=54), bile spillage during surgery (n=36), prolonged admission due to pain or malaise (n=17) or bleeding (n=10). Biliary complications (i.e. development of cholecystitis before

cholecystectomy, biliary pancreatitis) were reported in 4.9% of patients (n=55/361). Recurrent biliary colic with hospitalization occurred in 3.7% of patients (n=42/361).

Table 2. Patient outcomes in terms of the Textbook Outcome criteria

	Total (N=1124)
No recurrent biliary colic with hospitalization[b], n (%)	1082 (96.3)
Biliary complication, n (%)	55 (4.9)
Development of cholecystitis before cholecystectomy, n (%)	19 (1.7)
Choledocholithiasis, n (%)	30 (2.7)
Cholangitis, n (%)	0
Biliary pancreatitis, n (%)	6 (0.5)
Surgical complications, n (%)	154 (13.7)
Postoperative pain with prolonged hospital stay, n (%)	17 (11.5)
Wound infections, n (%)	54 (35.1)
Bile spillage with drain placement and/or prolonged hospital stay, n (%)	36 (23.4)
Bleeding during surgery, n (%)	10 (6.5)
Bile duct injury [d]	
Minor injury, n (%)	8 (0.5)
Major injury, n (%)	4 (0.3)
Pain-free or relief of abdominal pain, n (%)[e]	951 (84.6)
Composite Textbook Outcome rate, n (%)	763 (67.9)

[a] TO-criteria: no recurrent of biliary colic with hospitalization, absence of biliary complications, and absence of surgical complications, and free or relief of Upper Abdominal Pain (UAP)
[b] Visit at the emergency department or clinical admission for simple anaesthetics.
[c] Surgical complications and cardiovascular complications were classified in accordance of the CDC classification (20)
[d] Bile duct injury is classified in minor or major injury (16)
[e] Pain-free was defined as VAS ≤4. Pain relief was defined as reduction VAS pain score ≥4 points. ([5])

Differences at baseline between patients with and without TO

Individual baseline characteristics of patients with and without TO were compared (Table 1). Sex and BMI were evenly distributed within groups. Patients who achieved TO reported more frequent severe pain attacks at baseline (89.4% vs. 81.7%, p<.001). Patients who achieved TO reported more often presence of a biliary colic at baseline (78.6% vs, 68.4%, p<.001).The VAS Pain score was statistically significant different (8.0 IQR 6.6-9.0 vs 8.0 IQR 6.4-9.0, p=0.044) although median and IQR were comparable. Patients without TO were more likely to use non-opioid analgesics (56.4% vs. 62.6%, p=0.047) and reported more frequently episodes of pain (>1x/months) (37.1% vs. 52.0%, p<.001).

Factors associated with TO

The following variables were included in the regression analyses to assess independent predictive factors: age, sex, BMI, history of abdominal surgery, biliary colic, use of simple anaesthetics, pain radiating to the back, urge to move during pain attack, frequency of pain more than once a month, nausea and/or vomiting, heartburn, abdominal bloating, diarrhoea, and difficult defaecation.

Independent predictive factors for achieving TO after cholecystectomy were investigated (Table 3). Multivariable analysis showed that presence of biliary colic (OR 1.56, 95%CI 1.16-2.10, p=0.003), and nausea and/or vomiting (OR 1.33, 95%CI 1.1-1.74, p=0.039) were independently associated with achieving TO. Use of non-opioid analgesics (OR 0.76, 95%CI 0.57-0.99, p=0.043), frequency of pain more than once a month (OR 0.56, 95%CI 0.53-0.73, p<.001) were negatively associated with achieving TO.

Table 3. Univariable and multi-variable analysis of the associated factors achieving TO after cholecystectomy

Variable	Univariable OR (95% CI)	P-value	Multivariable OR (95% CI)	P-value	Regression coefficient
Baseline characteristics					
Age	0.999-1.009	0.906	0.994-1.014	0.460	1.004
Sex (female)	0.754-1.348	0.958	0.816-1.545	0.477	1.123
BMI	0.959-1.007	0.156	0.959-1.010	0.227	0.984
History of abdominal surgery	0.638-1.066	0.141	0.666-1.144	0.326	0.873
Abdominal pain					
VAS Pain score	0.970-1.082	0.392	0.932-1.054	0.757	0.990
Biliary colic by ROME III-criteria*	1.282-2.251	<.001	1.158-2.096	0.003	1.558
Use of non-opioid analgesics	0.597-0.997	0.047	0.574-0.992	0.043	0.755
Pain radiating to the back	0.644-1.165	0.343	0.703-1.374	0.869	0.973
Urge to move during pain attack	0.959-1.727	0.093	0.818-1.539	0.476	1.122
Pain frequency >1/month	0.419-0.705	<.001	0.427-0.731	<.001	0.559
Functional symptoms					
Nausea and/or vomiting	1.035-1.712	0.026	1.014-1.735	0.039	1.326
Heartburn	0.676-1.187	0.427	0.676-1.286	0.676	0.934
Abdominal bloating	0.801-1.325	0.817	0.800-1.437	0.639	1.073
Diarrhea	0.827-1.649	0.379	0.892-1.874	0.174	1.293
Difficult defecation	0.603-1.146	0.259	0.609-1.218	0.399	0.862

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); IQR, interquartile range; VAS, visual analog scale.

*All three ROME criteria included: severe pain in attacks, located in right upper quadrant or epigastric region and duration of pain longer than 15-30 minutes.

DISCUSSION

The present study assessed TO as post-hoc analysis in patients in two multicenter Dutch trials. TO is achieved in two-thirds of patients who underwent LC for uncomplicated symptomatic cholecystolithiasis. Considering the large numbers of cholecystectomies performed annually, this outcome highlights the need for improvement in patient selection. Selection should focus on the prevention of persistent pain, as this is the main factor contributing to a low TO rate. This post-hoc analysis in patients included in two multicenter Dutch trials show that the presence of biliary colics and nausea/vomiting as complaints at baseline are independent predictors for achieving TO after LC. In contrast, use of non-opioid analgesics and pain frequency >1 event/month are independently associated precluding TO.

LC is not a one-size-fit-all procedure, and well-defined selection criteria are crucial for optimal patient reported outcomes. In the majority of patients, typical biliary colic is effectively resolved after surgery. (5) The current study shows nausea and/or vomiting are associated with reaching TO following cholecystectomy, which are often reported as a part of biliary colic. (21) One third of patients with uncomplicated cholecystolithiasis report persistent UAP after cholecystectomy. (4) The literature suggests that several gastrointestinal symptoms deriving from disease etiologies other than gallstones are responsible for the development of persisting UAP. FGID have a prevalence of 20-30% among patients with uncomplicated cholecystolithiasis. (22, 23) Symptomatic cholecystolithiasis and FGID may be very similar in presentation and pain characteristics. (3, 24) These similarities complicate diagnosing the condition responsible for a patient's complaints and, as a result, possibly lead to abdominal pain being improperly attributed to gallstones and may influencing the choice for cholecystectomy.

The clinical workup for patients with abdominal pain and suspected gallstones generally starts with an abdominal ultrasound (US). In many care systems, US is requested by the general practitioner, and if gallstones are present the patient is subsequently referred to the surgical outpatient clinic. Although ultrasound is non-invasive and relatively inexpensive, a recent study reported a diagnostic yield of 36% for the detection of gallstones by US in patients with abdominal pain and clinical suspicion of gallstones according to the general practitioner. (25) To aid general practitioners in selecting patients for abdominal US, a model to predict presence of gallstones was developed. (25) Predictors for the presence of gallstones were increased pain, frequency of pain less than weekly, the presence of biliary colic, and the absence of heartburn. Subsequently, selection for surgery during shared-decision making at the surgical outpatient clinic requires another tool to aid patients and surgeons. Therefore, another online decision tool was recently developed to predict the probability that a patient will have significant pain reduction after cholecystectomy. (5) This model considers patient characteristics, pain scores,

surgical history and absence of heartburn. It is relevant to emphasize that both the decision tools for the general practitioner and the surgeon include patient characteristics, pain, and the presence of FGID.

Adequate treatment for patients with non-typical biliary symptoms is challenging. A recent study showed worse outcomes of surgery in 401 patients with abdominal pain and gallstones if a FGID was present. (8) Treatment for FGID is not as straightforward as cholecystectomy and includes physical and psychological factors. However, there is a lack of understanding of the role of conservative treatment, which typically consists of a multifactorial approach, including informing and educating patients on the relief of symptoms. The recent TRIODe trial (NCT03205319) in patients with unaffirmed dyspepsia showed that a personalized education tool is effective in reassuring patients about symptoms and reducing the number of gastroscopies by 40%. (26) A personalized self-help guide for patients with UAP with an absence of typical symptoms of gallstone disease may help patients to make better-informed decisions and improve patient-reported outcomes. A randomized controlled trial (NCT06002516) is currently underway for patients with UAP due to functional dyspepsia, irritable bowel syndrome and gallstone disease. The intervention arm will consist of a self-help guide combined with a lifestyle clinic visit. The hypothesis tested in this trial is that providing education on symptoms and lifestyle assessment to patients may lead to a reduction in unnecessary treatment and diagnostics interventions (i.e. cholecystectomy, gastroscopy, and colonoscopy) while also improving patient-reported outcomes in terms of abdominal symptoms and satisfaction. TO will be an important outcome parameter in both arms of this trial.

We acknowledge that this study comes with some limitations. First, the definition of TO was determined after both trials were conducted and with the post-hoc design of present study this may introduce bias. Secondly, defining a successful outcome after surgery for the treatment of uncomplicated cholecystolithiasis remains a subject of ongoing debate. In our questionnaires we evaluate the presence of abdominal pain by use of the VAS, however the type of persisting pain and the impact on the patient's overall quality of life were not evaluated. (27) Third, participants were enrolled from two prospective trials which may introduce a risk of bias. However, both studies applied identical inclusion criteria and hospitals included patients in both cohorts but in different time intervals.

In conclusion, the consensus-based TO may be a future tool to assess quality outcomes for treatment of patients with symptomatic uncomplicated cholecystolithiasis. The present study illustrates a relatively low success rate in achieving TO, endorsing a more optimized selection for cholecystectomy. TO after cholecystectomy is associated with biliary colic and nausea/vomiting at baseline, but surgery should be reconsidered in patients with more frequent pain and use of non-opioid analgesics that could be related to cholecystolithiasis. The low incidence of biliary complications display the possibility to treat patients with atypical symptoms conservatively and postpone surgery.

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CHAPTER

8

Short disease-specific quality of life questionnaire for patients with uncomplicated symptomatic cholecystolithiasis: Gall-Questionnaire

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BJS Open 2025



ABSTRACT

BACKGROUND Questionnaires measuring disease-specific quality of life in patients with uncomplicated cholecystolithiasis often perform sub optimally. This study aimed to develop and validate a concise questionnaire for assessing quality of life in these patients.

METHODS In phase I, surgeons, researchers, and a medical psychologist selected questions from four existing validated surveys to create the new Gall-Q questionnaire. In phase II, the psychometric properties of the Gall-Q were evaluated in a prospective multicentre study. Patients (≥18 years) with uncomplicated cholecystolithiasis referred for cholecystectomy were included. The PAGI-SYM (upper abdominal symptoms) and HADS (anxiety, depression, and distress) questionnaires were used to assess construct validity.

RESULTS Phase I resulted in the Gall-Q with 15 items across three subscales: biliary pain, non-biliary abdominal symptoms, and daily functioning. In phase II, 156 patients completed the Gall-Q, PAGI-SYM, and HADS. Factor analysis supported a three-factor structure. The internal consistency reliability of the 15-item Gall-Q was 0.710. Removing two low-performing items increased the Cronbach's alpha to 0.786. Construct validity showed a strong correlation between the Gall-Q and PAGI-SYM (0.737, CI95% 0.656-0.802), a moderate correlation with the HADS-Anxiety subscale (0.509, CI95% 0.382-0.616), and a small correlation with the HADS-Depression subscale (0.337, CI95% 0.190-0.469).

CONCLUSION The 13-item Gall-Q is a validated and reliable instrument for assessing the impact of uncomplicated cholecystolithiasis on disease-specific quality of life. The Gall-Q can refine personalized care and enhance treatment outcomes for individuals with uncomplicated cholecystolithiasis

INTRODUCTION

Gallstones are common in the Western population. Each year in the United Kingdom, over 70 000 patients are diagnosed with uncomplicated symptomatic gallstone disease. (1) Uncomplicated cholecystolithiasis is characterized by biliary colics, defined as acute, severe abdominal pain in the right upper quadrant or epigastrium, lasting 15-30 minutes or longer. (2, 3) Pain attacks and possible associated anxiety may cause reduced quality of life in patients with gallstones. (4) However, in most patients gallstones remain without typical symptoms and are not the primary cause of abdominal pain. Recently, the PERFECT-trial showed that more than one-third of patients with uncomplicated cholecystolithiasis fulfil the criteria for Functional Gastrointestinal disorders (FGID). (5) FGIDs generally overlap with similar pain characteristics and complicate diagnosis of the condition responsible for a patient's complaints.

Patient Reported Outcome Measures (PROMs) are often used to evaluate treatment success and impact on quality of life (QoL). PROMs reflect on treatment outcomes and burden of disease as experienced by patients. They can be used in research, for performance assessment and quality improvement, but also to improve communication and decision-making in clinical practice. (6) A recent international consensus-based study aimed to improve quality-assessment by defining a textbook outcome for patients with uncomplicated gallstone disease. The study involved patients and clinical experts from 81 countries and concluded that biliary pain, non-biliary abdominal symptoms, and no interference in daily functioning were the most important items to evaluate effect of treatment in patients with symptomatic gallstone disease. (7)

Several questionnaires, both generic and disease-specific, are currently being used to evaluate QoL in patients with abdominal pain and gallstones. The most frequently used questionnaires are the Short Form Health Status (SF-36, 36 items) and the Gastrointestinal quality of life index (GIQLI, 36 items). (8, 9) These questionnaires are of high quality in terms of psychometric properties, but inconvenient to use in everyday practice because of large number of items and lack specificity for symptomatic cholecystolithiasis. Daliya et al. critically appraised the development and validation of questionnaires for patients with gallstone disease. (10) The authors concluded that a disease-specific questionnaire such as the short form Otago questionnaire is limited in terms of reliability and that there is a need for a short but reliable instrument to assess disease-specific QoL in patients with abdominal complaints and gallstones. (11)

The present study aimed to develop a short questionnaire to assess disease-specific quality of life in patients with uncomplicated symptomatic cholecystolithiasis and to evaluate psychometric properties of this scale by examining floor-and-ceiling effects, structural validity, internal consistency, and construct validity (convergent and divergent

validity).

METHODS

Study design

The development and validation of the Gall-Q encompasses two phases. Phase I; selection of items and development of the Gall-Q questionnaire, and Phase II; evaluation of psychometric properties of the Gall-Q. Figure 1 presents a more detailed outline of the study phases.

Phase I: Gall-Q development and initial reliability estimates

Items were derived from four existing validated QoL questionnaires: EuroQol-5 Dimension-3 Level questionnaire (EQ-5D-3L), the Gastro Intestinal Quality of Life Index (GIQLI), the Gallstone Symptom List (GSL), and the Izbicki Pain Score (IPS). (8, 12, 13) During expert group meetings, all items were discussed and selected for inclusion in the Gall-Q based on expert opinion. These meetings were attended by surgeons, researchers and a medical psychologist with expertise in research on quality of life. Items were selected for three different subscales: 1. Biliary symptoms, 2. Non-biliary abdominal symptoms, 3. Daily functioning. The questionnaire consisted of 15 items on three dimensions (Tables S1).

Biliary symptoms: 5 items, four 5-points Likert scales ranging from 1 to 5, and 1 VAS pain scale ranging from 0-10.

Non-biliary abdominal symptoms: 6 items scored on a Likert scale from 1-5.

Daily functioning subscale: 4 items scored on a Likert scale from 1-5.

For all Likert scales, ranging from 1 to 5, higher scores indicate a heavier burden. The VAS ranges from 0 to 10, with a higher scores indicating more pain. The total score is the sum of all items (VAS-score divided by 2) and ranges from 14-74. Subscale scores can be computed by adding the scores of the individual items within the subscale. Total scores of the subscales are as follows: 1) Biliary symptoms: 4-24, 2) Non-biliary abdominal symptoms: 6-30, 3) Daily functioning: 4-20.

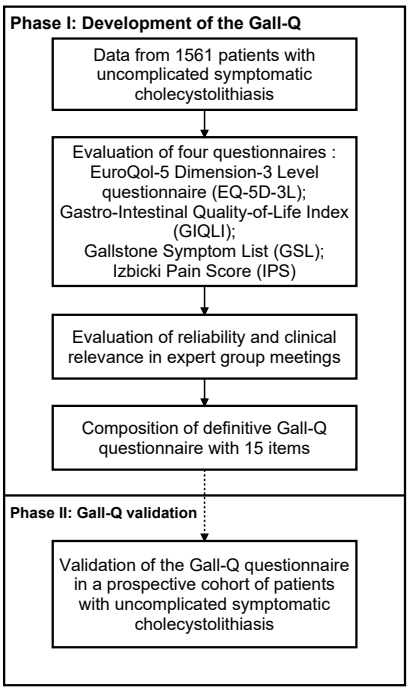

Figure 1. Flowchart of study design

Phase II: Validation of the Gall-Q

Study sample

Between December 2021 and November 2023, all consecutive eligible patients were invited to participate in the validation study. The study was conducted in two teaching hospitals in the Netherlands. Inclusion criteria were: patients aged between 18 and 95 with uncomplicated cholecystolithiasis and a new referral to a surgical outpatient clinic. Exclusion criteria were a history of complicated cholecystolithiasis (i.e., choledocholithiasis, acute cholecystitis, biliary pancreatitis, or cholangitis), active mental disorder or incompetence that influences reliability of questionnaire response, insufficient knowledge of the Dutch language.

The sample size was determined based on the requirements for performing exploratory factor analysis. We applied a threshold of 10 participants per item. (14) The version of the Gall-Q used during the validation phase comprised 15 items, resulting in a sample size of 150 participants (n ≥ 10 per item). A sample size of 150 patients is also sufficient to evaluate psychometric properties according to the Consensus-Based Standards for the Selection of Health Status Measurement Instruments (COSMIN) checklist. (15, 16)

Ethical considerations

All patients provided written informed consent, which was obtained during first consultation. This study was approved by the medical ethics commission (METC: 2021-8262) and approved by all boards of directors of the participating hospitals. This research was performed in accordance with the ethical standards of the updated Helsinki Declaration of 2013 and using the COSMIN-checklist.

Patient characteristics and questionnaires

Patient characteristics (i.e., sex, age, Body Mass Index (BMI)) and additional clinical data (history of abdominal surgery, concomitant abdominal disorders such as FGID), presence of a biliary colic were collected from electronic patient records. Selected treatment, laparoscopic cholecystectomy or conservative treatment strategy, at time of first visit was assessed.

Questionnaires were provided on paper during first consultation at the outpatient clinic. To evaluate construct validity, patients received two additional questionnaires besides the Gall-Q: The Patient Assessment of Gastrointestinal Disorders Symptoms Severity Index (PAGI-SYM) and the Hospital Anxiety and Depression Scale (HADS). (17, 18)

The PAGI-SYM consists of 20 items in 6 subscales: nausea/vomiting, postprandial fullness and early satiety, bloating, upper abdominal pain, lower abdominal pain, and heartburn/regurgitation. Severity of each symptom is rated using a 6-point Likert scale, ranging from 0 (none) to 5 (very severe), over a 2-week period. Total score is the mean of all subscales. A lower score indicates better health. (17) The HADS is a 14-item questionnaire developed to indicate the presence of anxiety and depression symptoms. Each item has different response options on a 4-point Likert scale (range 0 to 3), which results in two scales: the anxiety scale (HADS-A), indicating the level of anxiety and the depression scale (HADS-D), indicating the level of depression symptoms. (18) Total scores of both scales range from 0 to 21, where a higher score indicates a higher level of anxiety or depression symptoms.

Validity assessment and statistical analysis

Categorical data were summarized by frequencies and proportions. Continuous data were presented as mean with standard deviation when normally distributed or median with interquartile range (IQR) when non-normally distributed.

To assess floor- and ceiling effects, the mean, proportion of patients reporting minimum and maximum response categories were examined for the total score and the three subscales. Floor and ceiling effects were considered to be present if more than 15% of participants achieved either the lowest or the highest possible score. (19) To assess

internal consistency, Cronbach's alpha was calculated for the total questionnaire. Internal consistency was considered acceptable if Cronbach's alpha was between 0.70 and 0.95. (19) Spearman's correlations were calculated to assess convergent and divergent validity, correlations of ≥ 0.5 were considered large, 0.3-0.5 moderate, and 0.3 small. It was hypothesized that the Gall-Q would have a large positive correlation (≥ 0.5) with the PAGI-SYM as they were both assumed to measure upper abdominal symptoms (convergent validity).

Furthermore, it was hypothesized that the Gall-Q would have a small to moderate positive correlation (0.3-0.5) with the subscales depression and anxiety of the HADS as mental wellbeing is part of quality of life but not explicitly assessed in the Gall-Q. Structural validity was assessed by exploratory factor analysis, which was performed with orthogonal (varimax) and oblique rotations to examine factor structures. Kaiser-Meyer-Olkin test (KMO) with Bartlett's Test of Sphericity were used to assess suitability for exploratory factor analyses, the cut-off value for the KMO ≥ 0.7 and a p-value <0.05 for Bartlett's Test of Sphericity. Additionally, scree tests were used to determine the number of factors to retain. Patients with incomplete response to the questionnaires were excluded from analyses. Missing data was reported in percentages. For all analyses, IBM SPSS statistical software version 27.0 (SPSS Inc., Chicago, IL) was used.

RESULTS

Phase 1

During the expert group meetings, there was consensus that three subscales were relevant to be surveyed: biliary symptoms, abdominal symptoms and impact on daily functioning. All fifty questions of the EQ-5D, GIQLI, GSL, and IPS were reviewed, of which 14 questions were deemed most relevant and in accordance with the three subscales. No items from the EQ-5D were used, while 9 out of 36 were selected from the GIQLI, 3 out of 5 items from the GSL, and 2 out of 4 items from the IPS. Additionally, one more question was included to survey the onset of symptoms.

Phase 2

Sample descriptives

Between December 2021 and November 2023, 163 patients provided informed consent. Seven patients were excluded because of incomplete response to the questionnaires. In total, 156 patients were included for analyses in this study.

Demographics at baseline are shown in Table 1; 74.4% of patients were female (n=

116/156) and median BMI was 28.9 kg/m^2 (IQR 24.9-33.3). With regards to medical history, 23.7% (37/156) had a history of abdominal surgery. On a biliary colic was reported in 44.2% of patients (n= 69/156) and 7.7% of patients (n=12/156) were previously diagnosed with a FGID. Laparoscopic cholecystectomy was chosen as treatment at first consultation in 89.7% of patients (n= 140/156).

Table 1. *Baseline characteristics of included patients from electronic patient records.*

	N = 156
Sex, Female (%)	116 (74.4)
Age, mean (SD)	51.5 (15.7)
BMI, median (IQR)	28.9 (24.9-33.3)
History of abdominal surgery, yes (%)	37 (23.7)
Additional diagnosis of FGID, yes (%)	12 (7.7)
Biliary colic, yes (%)	69 (44.2)
Additional visit due to persisting symptoms, yes (%)	6 (3.8)
Chosen treatment at first visit, n cholecystectomy (%)	140 (89.7)

Questionnaire responses

Responses to the items in the three subscales are shown in Table 2. The median VAS pain score was 8.0 (IQR 7.0-9.0). Weekly biliary symptoms were reported by 36.5% of patients and 79.9% indicated that pain lasted for over 1 hour (79.9% (n= 124/156)). Patients reported abdominal fullness or bloating for at least some of the time (53.2% (n=83) and 60.9% (n=95), respectively). Obstipation, nausea/vomiting, and heartburn were reported less often (21.7% (n=34), 30.2% (n=47) and 22.5% (n=35) respectively).

Nearly half of the patients, 45.5% (n=71), reported an inability to work due to abdominal pain. Additionally, 37.2% (n=58) experienced anxiety related to abdominal pain, and 31.4% (n=49) were unable to complete daily activities due to gallstones.

Floor- and ceiling effects (more than 15% of participants achieving either the lowest or the highest possible score) were not observed. The mean of the total score of the Gall-Q was 42 points (range 19.5-65), no patients reported minimum or maximum scores. For the subscales, the mean score on biliary symptoms was 17.5 (range 5-24), one patient (0.6%) reported the minimal and one patient the maximal score. For abdominal symptoms the mean was 13.8 (range 6-28), 12 patients (7.3%) scored minimal possible points and no patients scored maximal. For daily functioning the mean was 10.8 (range 4-18), 1 patient (0.6%) scored minimal and no patients scored the maximum of 18. Histograms of the total score and scores on subscales can be found in supplementary files (Figure S1-S4).

Table 2. *Descriptive statistics of responses to the Gall-Q*

Biliary symptoms					
VAS, median (IQR)	**8.0 (7.0-9.0)**				
	No pain	*6 monthly*	*3 monthly*	*Monthly*	*Weekly*
Frequency of pain attacks, n (%)	3 (1.9)	21 (13.5)	36 (23.1)	39 (25.0)	57 (36.5)
	> 12 months	*6-12 months*	*1-6 months*	*1 week – 1 month*	*< 1 week*
Start of pain attacks, n (%)	51 (32.7)	23 (14.7)	51 (32.7)	25 (16.0)	6 (3.8)
	No pain	*<30 min*	*30 min – 1 hour*	*1-6 hours*	*6-24 hours*
Pain duration, n (%)	4 (2.6)	10 (6.4)	18 (11.5)	66 (42.3)	58 (37.2)
	Never	*A little of the time*	*Some of the time*	*Most of the time*	*All of the time*
Use of analgesics, n (%)	25 (16.0)	23 (14.7)	32 (20.5)	38 (24.4)	38 (24.4)
Abdominal symptoms					
	Never	*A little of the time*	*Some of the time*	*Most of the time*	*All of the time*
Abdominal pain last 2 weeks, n (%)	35 (22.4)	38 (24.4)	45 (28.8)	23 (14.7)	15 (9.6)
Abdominal fullness, n (%)	25 (16.0)	36 (23.1)	46 (29.5)	27 (17.3)	22 (14.1)
Abdominal bloating, n (%)	32 (20.5)	42 (26.9)	39 (25.0)	31 (19.9)	12 (7.7)
Obstipation, n (%)	85 (54.5)	37 (23.7)	23 (14.7)	10 (6.4)	1 (0.6)
Nausea and/or vomitus, n (%)	58 (37.2)	51 (32.7)	31 (19.9)	7 (4.5)	9 (5.8)
Heartburn, n (%)	84 (53.8)	37 (23.7)	21 (13.5)	12 (7.7)	2 (1.3)
Daily functioning					
	Not	*< 1 week*	*1 week – 1 month*	*1 month – 1 year*	*Permanently*
Inability to work, n (%)	85 (54.5)	42 (26.9)	10 (6.4)	10 (6.4)	10 (5.8)
	Never	*A little of the time*	*Some of the time*	*Most of the time*	*All of the time*
Anxiety, n (%)	58 (37.2)	40 (25.6)	33 (21.2)	10 (6.4)	15 (9.6)
Woke up at night, n (%)	35 (22.4)	48 (30.8)	23 (14.7)	9 (5.8)	41 (26.3)
Finishing daily activities, n (%)	7 (4.5)	21 (13.5)	21 (13.5)	43 (27.6)	64 (41.0)

Internal consistency

Table 3 shows the item analyses on questionnaire items. Internal consistency reliability for the Gall-Q with all 15 items was 0.710. Removal of item 15 ("impaired in daily activities") resulted in a Cronbach's alpha of 0.774 (14 items). Further exclusion of item 2 ("start of pain attacks") led to an improved Cronbach's alpha of 0.786, indicating good internal consistency reliability. These items were eliminated after performing poor in terms of reliability, but also during factor analyses, as described below.

Table 3. Reliability scores during the analyses of the Gall-Q

Items	Outcomes
Reliability	**Cronbach's alpha**
Gall-Q with 15 items	0.710
Gall-Q with 14 items (item 15 removed)	0.774
Gall-Q with 13 items (items 2 and 15 removed)	0.786
Construct validity*	**Correlation**
Gall-Q versus PAGI-SYM	0.737 (0.656-0.802)
Gall-Q versus HADS-Anxiety	0.509 (0.382-0.616)
Gall-Q versus HADS-Depression	0.337 (0.190-0.469)

**Construct validity was tested including 13-items (after item 2 and 15 were removed)*

Structural validity

An exploratory factor analysis using varimax rotation to validate distinct subscales was performed on the 15 items of the Gall-Q. Adequacy measures of the 15-item set of the Gall-Q, such as the Kaiser-Meyer-Olkin measure (KMO=0.798) and Bartlett's Test of Sphericity (P<.001) confirmed the dataset's suitability for an exploratory factor analysis. The factor analysis resulted in a four-factor model. However, the interpretation of the fourth factor remained ambiguous. In combination with the results on internal consistency reliability, items 2 and 15 were excluded from the questionnaire, reducing the analysed items to 13.

Adequacy measures of the 13-item set of the Gall-Q again confirmed suitability for exploratory factor analysis (KMO=0.782 and Bartlett's Test of Sphericity P<.001). Examination of the scree plot (see Figure 2) indicated a noticeable break occurring after either the second or third factor. Consequently, the most appropriate solution appeared to be a three-factor model, as intended. Moreover, except for frequency of pain attacks and obstipation, all items presented in the factors as planned in advance. Cross-factor loading was observed in item 4 (use of analgesics) and item 8 (abdominal bloating). Detailed outcomes from the factor analyses are presented in Table 4.

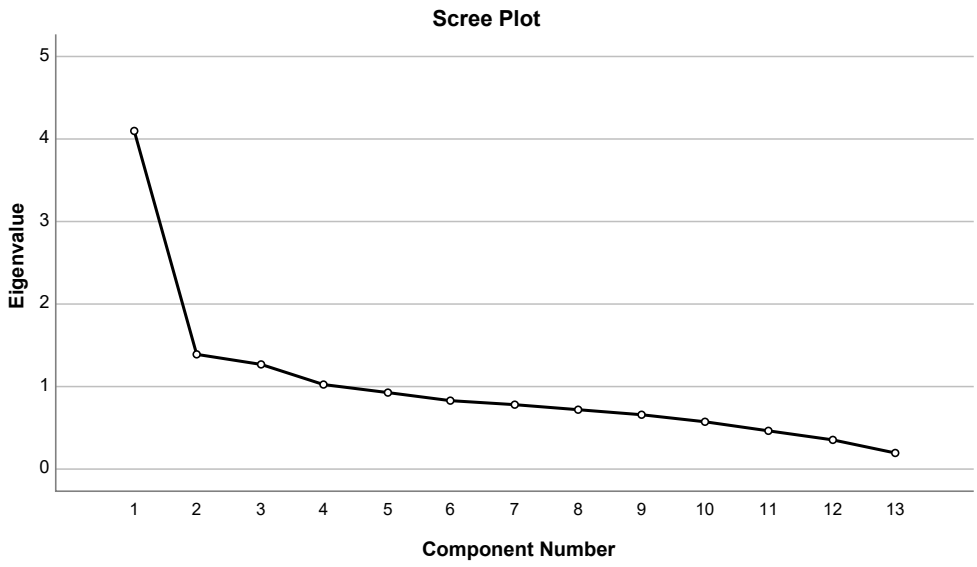

Figure 2. Scree Plot of the confirmatory factor analysis of the Gall-Q

Table 4. *Factor loadings of the Gall-Q including 13 items*

Item		Factor 1	Factor 2	Factor 3
7	*Abdominal fullness*	0.823		
6	*Abdominal pain last 2 weeks*	0.777		
8	*Abdominal bloating*	0.673	0.397	
1	*Abdominal pain last 6 months*	0.673		
10	*Nausea and/or vomitus*	0.615		
11	*Heartburn*	0.518		
14	*Woke up at night*		0.690	
13	*Anxiety*		0.604	
9	*Obstipation*		0.590	
12	*Disease-related inability to work*		0.589	
5	*VAS pain scale*			0.706
3	*Pain duration*			0.648
4	*Use of analgesics*	0.439		0.645

Construct validity

The correlations between the PAGI-SYM and the Gall-Q and between the HADS and the Gall-Q were assessed to test the hypothesis that the Gall-Q and the PAGI-SYM would have a strong correlation, while the HADS and the Gall-Q would have a small to moderate positive correlation.

An expected large correlation between Gall-Q and PAGI-SYM was observed, with a correlation coefficient of 0.737 (CI95% 0.656-0.802). Likewise, an expected moderate correlation between the Anxiety scale of the HADS and the Gall-Q of 0.509 (CI95% 0.382-0.616) and a small correlation with the HADS-Depression scale of 0.337 (CI95% 0.190-0.469) were observed.

DISCUSSION

Our study aimed to create a concise disease-specific quality of life questionnaire for patients with uncomplicated symptomatic cholecystolithiasis, the Gall-Q. We developed and validated a 13-item psychometric instrument in 156 patients. The Gall-Q effectively measures disease-related quality of life in three subscales: 1) biliary symptoms, 2) non-biliary abdominal symptoms, 3) daily functioning. The questionnaire showed good internal consistency and construct validity.

The expression of symptomatic gallstone disease varies, ranging from non-biliary abdominal symptoms to typical biliary colic, which develops in only 20% of patients. The choice for surgery is often based on the impact of symptoms on quality of life, in terms of pain or anxiety for potential complications. Laparoscopic cholecystectomy is the recommended treatment to resolve typical biliary colic and is effective in 95% of patients. Outcomes of cholecystectomy for symptomatic cholecystolithiasis are uncertain, as pain persists in up to 40% of patients for months or even years post-surgery. (20) To accurately evaluate complaints and disease-burden, it is important to use disease specific and validated questionnaires. Over the past decades, the use of PROMs in medical research have increased. (21) PROMs have the potential to more precisely measure clinical reality of patients and the impact of a disease. (6) For uncomplicated symptomatic gallstone disease, many different questionnaires have been used to evaluate complaints and disease burden. In recent years, several studies have been performed on the use of questionnaires for patients with gallstone disease. (10) In 2019, Daliya et al assessed the quality of 6 validation studies (3 different questionnaires: 1) Gastro-Intestinal Quality of Life Index; GIQLI, 2) Gallstone Impact Checklist; GIC, 3) Otago Gallstones Condition Specific Questionnaire; CSQ) and found them to be of poor methodological quality. (8, 11, 22) In addition to the conclusions of Daliya et al., these questionnaires have other shortcomings. The GIQLI is well-known and often used, but it is not specific to

gallstone disease and extensive with 36 questions. The GIC is not suitable for daily use, because it comprises 41 items. The CSQ consists of just 12 items, but fails to characterize the nature of the pain and allocates all complaints to gallstones, without surveying the presence of functional disorders. Other systematic reviews found that generic questionnaires (such as the EQ-5D and the SF-36) have been used to evaluate abdominal complaints and QoL, but these of course are not specific to gallstone disease. (23, 24) With the validated Gall-Q questionnaire, a concise set of 13 questions now exists, covering biliary symptoms, non-biliary abdominal complaints, and daily functioning. The Gall-Q enables the evaluation of the impact of uncomplicated gallstone disease on quality of life.

The availability of the present psychometric instrument is also a step forwards in the shared decision-making process for patients with uncomplicated cholecystolithiasis. Mediocre outcomes in terms of persistent pain after cholecystectomy are mainly reported in patients with gallstones who meet criteria for underlying FGID, as these disorders are not resolved by LC. Shared decision-making between patients and clinicians before and during first consultation is therefore necessary, especially in patients experiencing abdominal pain, gallstones, and signs of FGID. To determine the emphasis of treatment, it is crucial to clarify which condition the patient is suffering from the most, whether it be biliary colic or atypical abdominal pain associated with the presence of gallstones. The Gall-Q can aid in identifying patients symptoms with the highest impact on QoL and guide treatment decisions to achieve better patient outcomes.

This study comes with several strengths. First, a pragmatic approach was adopted following the COSMIN checklist, selecting items based on reliability, validity from different questionnaires, to accurately reflect the different expression of this disorder. Second, it fills a knowledge gap in the literature by developing a short and a reliable instrument to determine the impact of symptomatic cholecystolithiasis on quality of life. The fact that external validity of the Gall-Q was confirmed increases the generalizability. This study also has some limitations. The Gall-Q has, for now, only been validated in a Dutch population, which limits its international applicability. Translation and validation of the English version is underway. Second, the questionnaire was only designed to assess the disease-related quality of life in patients with uncomplicated cholecystolithiasis. For patients with (a history of) complicated cholecystolithiasis this questionnaire may therefore not be sufficient.

Much is to gain in the treatment and evaluation of symptomatic gallstone disease. The use of a single validated questionnaire allows for the determination of disease-specific quality of life in this extensive group of patients. Besides the use in research, the Gall-Q can also be used in daily practice to facilitate shared decision-making between clinicians and patients. The employment of the Gall-Q instrument ensures a validated meas-

urement of the disease-related quality of life and the multidimensional expression of uncomplicated cholecystolithiasis.

In conclusion, disease-related quality of life in patients with uncomplicated cholecystolithiasis can be assessed with the newly developed and validated Gall-Q. The Gall-Q can be applied in scientific research, may assist clinicians in their clinical work-upand represents a stride towards enhancing tailored care for patients experiencing symptomatic cholecystolithiasis.

SUPPLEMENTARY TABLES AND FIGURES

Supplementary Table S1:
Gall-Q, original English questions from the different questionnaires and Dutch translation.

How often do you experience abdominal pain in the last 6 months?	Hoe vaak heeft u gemiddeld een aanval van pijn in uw buik gehad in het laatste half jaar?
When did the pain attacks start?	Hoe lang geleden zijn de pijnaanvallen begonnen?
How long does the pain usually last?	Hoe lang duurde(n) de aanval(len) van pijn in uw buik?
How often do you use pain medication to manage your pain?	Hoe vaak gebruikt u pijnstilling als u een aanval van deze buikpijn heeft?
How severe is your pain when it occurs? (Often measured using a numerical rating scale from 0 to 10)	Geef op onderstaande schaal aan hoeveel pijn u (gemiddeld) heeft tijdens een pijnaanval
How often during the past 2 weeks have you had pain in the abdomen?	Hoe vaak heeft u in de afgelopen 2 weken pijn in uw buik gehad?
How often during the past 2 weeks have you had a feeling of fullness in the upper abdomen?	Hoe vaak heeft u in de afgelopen 2 weken een vol gevoel boven in de buik gehad?
How often during the past 2 weeks have you had bloating (sensation of too much gas in the abdomen)?	Hoe vaak heeft u in de afgelopen 2 weken een opgeblazen gevoel (gevoel van te
How often during the past 2 weeks have you been troubled by constipation?	Hoe vaak heeft u in de afgelopen 2 weken last gehad van verstopping?
How often during the past 2 weeks have you been troubled by nausea?	Hoe vaak heeft u in de afgelopen 2 weken last gehad van misselijkheid?
How often during the past 2 weeks have you been troubled by heartburn?	Hoe vaak heeft u in de afgelopen 2 weken last gehad van een brandend gevoel op de borst?
How much does your disease-related pain interfere with your ability to work?	Bent u arbeidsongeschikt (geweest) door de pijn?
How often during the past 2 weeks have you been nervous or anxious about your illness?	Hoe vaak bent u in de afgelopen 2 weken gespannen of angstig geweest over uw galsteenlijden?
Over the past week, have you woken up in the night?	Hoe vaak bent u in de afgelopen 2 weken 's nachts wakker geworden door de pijn?
During the past 2 weeks, how often have you been able to complete your normal daily activities (school, work, household)?	Hoe vaak heeft u in de afgelopen 2 weken uw normale bezigheden kunnen afmaken (bijvoorbeeld school, werk, huishouden)?

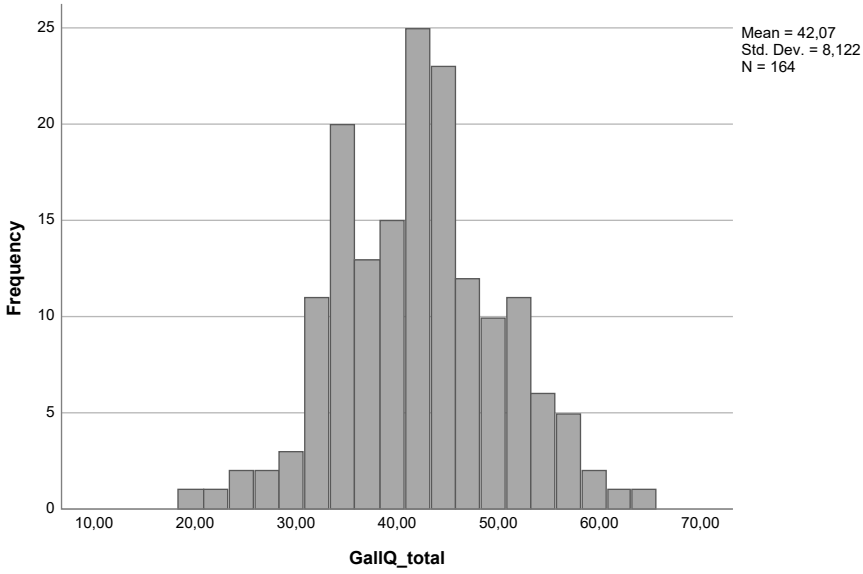

Figure S1. Histogram of the total score on the Gall-Q

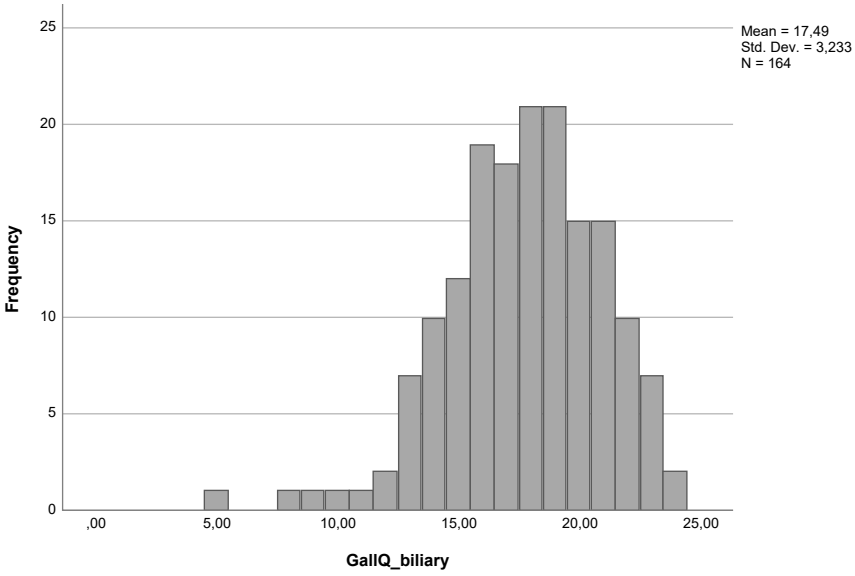

Figure S2. Histogram of the biliary subscale of the Gall-Q

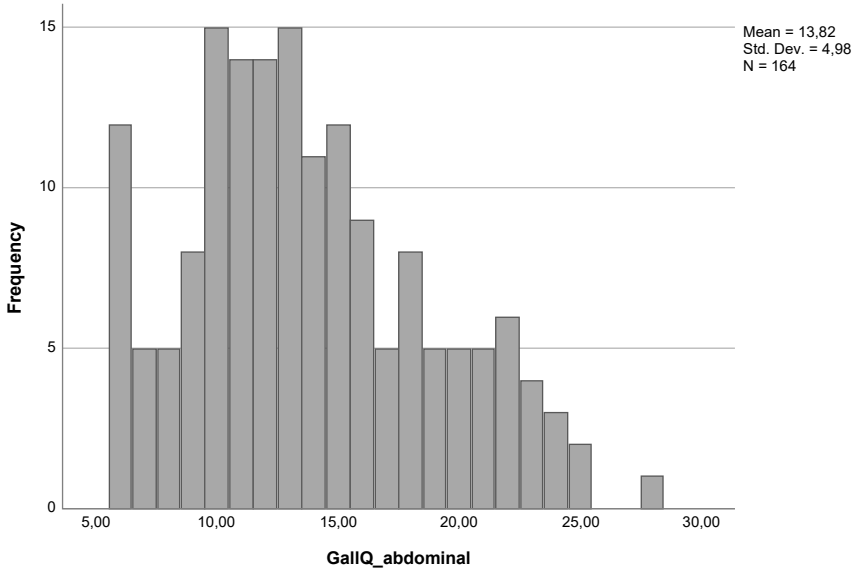

Figure S3. Histogram of the abdominal subscale of the Gall-Q

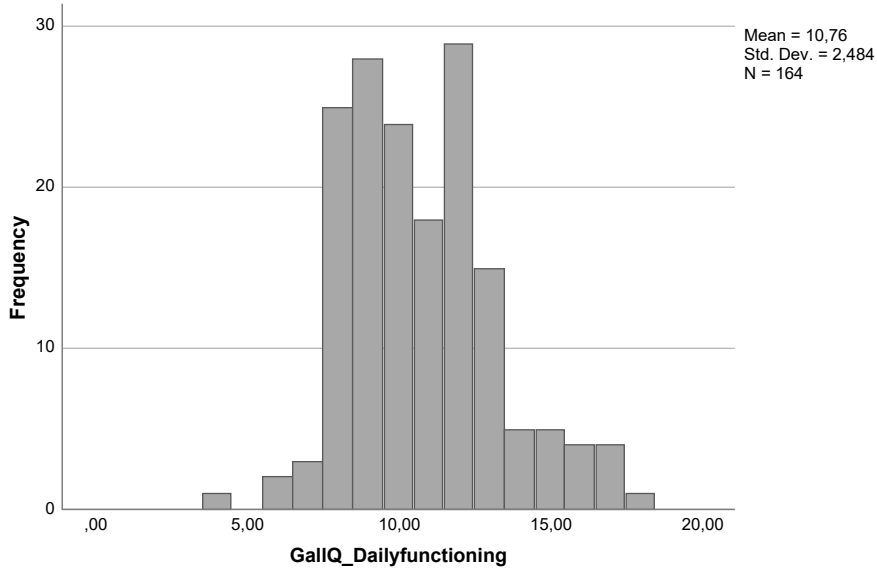

Figure S4. Histogram of the daily functioning subscale of the Gall-Q

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PART III

Shared decision-making



CHAPTER

9

Evaluation of a shared decision-making strategy with online decision aids in surgical and orthopaedic practice: Study protocol for the E-valuAID, a multicentre study with a stepped-wedge design.

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BMC Medical Informatics and Decision Making 2021



ABSTRACT

BACKGROUND Inguinal hernia repair, gallbladder removal, and knee- and hip replacements are the most commonly performed surgical procedures, but all are subject to practice variation and variable patient-reported outcomes. Shared decision-making (SDM) has the potential to reduce surgery rates and increase patient satisfaction. This study aims to evaluate the effectiveness of an SDM strategy with online decision aids for surgical and orthopaedic practice in terms of impact on surgery rates, patient-reported outcomes, and cost-effectiveness.

METHODS The E-valuAID-study is designed as a multicentre, non-randomized stepped-wedge study in patients with an inguinal hernia, gallstones, knee or hip osteoarthritis in six surgical and six orthopaedic departments.

The primary outcome is the surgery rate before and after implementation of the SDM strategy. Secondary outcomes are patient-reported outcomes and cost-effectiveness.

Patients in the usual care cluster prior to implementation of the SDM strategy will be treated in accordance with the best available clinical evidence, physician's knowledge and preference and the patient's preference. The intervention consists of the implementation of the SDM strategy and provision of disease-specific online decision aids. Decision aids will be provided to the patients before the consultation in which treatment decision is made. During this consultation, treatment preferences are discussed, and the final treatment decision is confirmed. Surgery rates will be extracted from hospital files. Secondary outcomes will be evaluated using questionnaires, at baseline, three, and six months.

DISCUSSION The E-valuAID-study will examine the cost-effectiveness of an SDM strategy with online decision aids in patients with an inguinal hernia, gallstones, knee or hip osteoarthritis. This study will show whether decision aids reduce operation rates while improving patient-reported outcomes. We hypothesize that the SDM strategy will lead to lower surgery rates, better patient-reported outcomes, and be cost-effective.

INTRODUCTION

Inguinal hernia repair, gallbladder removal, and knee- and hip replacement are routine and elective surgeries. While international guidelines advocate surgery in the majority of patients, a wait-and-see policy is justified in selected cases. (1-3) Although surgery is associated with quick symptom relief, long term outcomes are sometimes less favourable. (4-14) Because of the elective nature of these interventions, treatment decision depends on multiple factors, such as the severity of symptoms, organizational structures, and physicians' and patients' preferences. (15) Some of these factors have a role in inappropriate care, unwarranted practice variation, and higher costs. (16, 17)

Shared decision-making (SDM) leads to more appropriate care. (18-20) Allowing patients to have a more active role in their treatment decision results in a better consultation. (17) SDM balances empirical evidence, professional's expertise and patient's values. (21) In the case of SDM, clinicians need to provide patients with high-quality and balanced information. Clinicians need to assess the patients' values and preferences, and assist and empower patients in their process of decision-making. (22, 23) To support the SDM process, decision aids (DAs) are used. DAs are tools providing evidence-based information on the different treatment options to improve the disease-specific knowledge of the patient, while exploring patient values. (24-26) In general, the use of DAs leads to better informed patients, who are able to select a choice of treatment based on accurate risk perceptions, who can make better value-congruent choices and have less decisional conflict. (25, 27) The possibility that patients will opt for less invasive treatment choices will lower the costs and are potential benefits of SDM from a patient and societal perspective. (25)

The objective of this study is to evaluate the effect of an SDM strategy by using online DAs, specifically designed for patients who are eligible for inguinal hernia repair, gallbladder removal, knee- or hip replacement. This study will compare the SDM strategy to usual care, in terms of surgery rates, patient-reported outcomes, and cost-effectiveness. We hypothesize that the SDM strategy will reduce surgery rates, while patient-reported outcomes improve. The outcome of the E-valuAID-study will clarify if SDM with the use of DAs is beneficial for the patient and our healthcare system.

METHODS

The study protocol is designed in accordance with the CONsolidated Standards Of Reporting Trials (CONSORT) extension for stepped-wedge cluster randomized trials. (28) The study has been registered in the Netherlands National Trial Register (NTR) on the 22nd of January 2020 (Trial: NL8318, https://www.trialregister.nl/trial/8318).

Design

The E-valuAID is a multicentre, non-randomized stepped-wedge study in patients with an inguinal hernia, gallstones, knee- or hip osteoarthritis. The DAs will be implemented stepwise in six surgical and six orthopaedic departments in the Netherlands. Departments implement the DAs at different timepoints and will have different control and intervention periods. Therefore, the stepped-wedge design allows for comparisons within and between departments, and comparisons over time (Figure 1). Three additional control hospitals will be included to investigate time trends in surgery rates for both surgical and orthopaedic departments across the entire study, without implementing DAs. Data collection began on July 1, 2020, and each centre will include consecutive eligible patients for two years (Figure 1).

	1-3 Months	4-6 Months	7-9 Months	10-12 Months	13-15 Months	16-18 Months	19-21 Months	22-24 Months
Cluster[a] 1	C[b]	I[c]	I	I	I	I	I	I
Cluster 2	C	C	I	I	I	I	I	I
Cluster 3	C	C	C	I	I	I	I	I
Cluster 4	C	C	C	C	I	I	I	I
Cluster 5	C	C	C	C	C	I	I	I
Cluster 6	C	C	C	C	C	C	I	I

Figure 1, Stepped-wedge design on hospital level (primary outcome, surgery rates).
a A cluster consists of an outpatient clinic of surgery and an outpatient clinic of orthopaedics.b C= Control (usual care). c I= Intervention (SDM strategy with online DAs)

Study population

The study aims to include all patients above the age of 18 who are referred to the outpatient clinic of participating departments, with one of the following conditions: an inguinal hernia, abdominal pain and ultrasound proven gallstones, knee- or hip osteoarthritis. Eligibility criteria are presented in Table 1. The secondary outcomes will be assessed in all eligible patients who agree to fill out the questionnaires.

Table 1. Eligibility criteria

Inclusion criteria	Age ≥ 18 years One of the following conditions: inguinal hernia, gallstones, knee- or hip osteoarthritis Access to the internet Sufficient command of the Dutch language to complete decision aids and fill out questionnaires.
General exclusion criteria	Current treatment for malignancy Expected lifespan < 12 months Pregnancy
Condition related exclusion criteria	
Inguinal hernia	Recurrent or complicated inguinal hernia (e.g. incarcerated hernia, strangulation, ileus)
Gallstones	Complicated gallstone disease (e.g. cholecystitis, choledocholithiasis, biliary pancreatitis)
Knee- or hip osteoarthritis	Early-stage osteoarthritis Earlier arthroplasty

Patient recruitment

Screening for eligibility will be performed by the local nurse practitioner, surgeon, or involved study researcher. Patients will be provided with information about the study, asked to participate, and informed consent will be obtained.

Outcomes

The primary outcome of the E-valuAID-study is the percentage of patients undergoing surgery within six months after first presentation at the outpatient clinic. Secondary outcomes are patient-reported outcomes and cost-effectiveness of the SDM strategy. Figure 2 provides an overview of the clinical pathway, data collection, and the timeline in which the DA and questionnaires are provided.

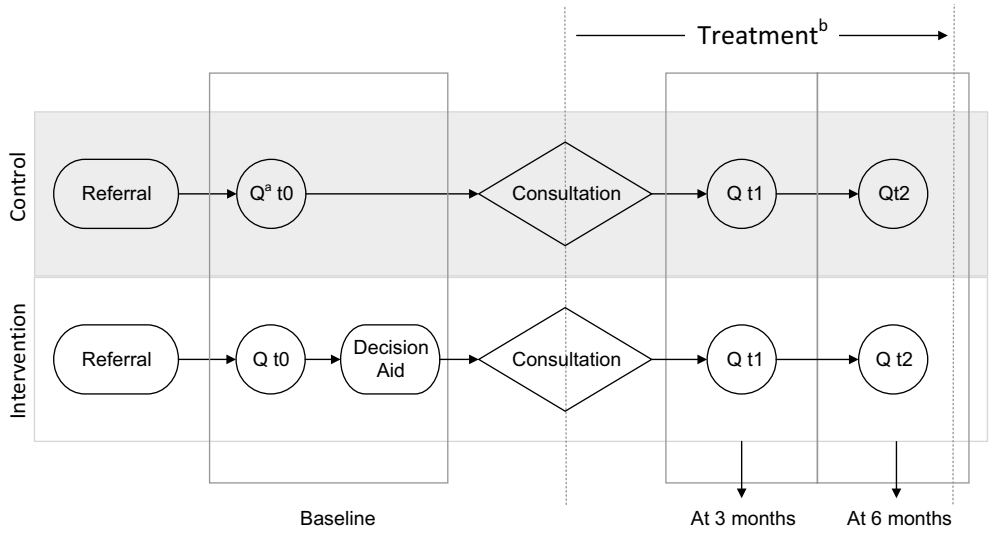


Figure 2. Clinical pathway and data collection timeline on patient level (secondary outcomes). a Q: Questionnaire. b The definitive treatment, conservative or surgery, will be assessed six months after inclusion.

Control group

In the control group, that is before implementation of the SDM strategy, all participating departments will reach treatment decision according to usual care. Usual care consists of treatment decisions based on clinical information (i.e. severity of symptoms, medical history, physical examination, and medical imaging), the physician's knowledge and experience, as well as both the patient's and physician's preferences.

Intervention group

At a pre-determined timepoint illustrated in Figure 1, the SDM strategy will be implemented at department level and the department moves to the intervention phase. Details on the implementation are described below. In the intervention phase, an online DA is provided to each patient before consultation in which treatment decision is made (Figure 2).

The condition-specific DAs are developed in accordance with the International Patient Decision Aid Standards (IPDAS) (24, 26) and in collaboration with the Dutch Society for Surgery (Dutch: NVvH, Nederlandse Vereniging voor Heelkunde), Dutch Orthopaedic Association (Dutch: NOV, Nederlandse Orthopaedische Vereniging), the Netherlands Patients Federation (Dutch: Patiëntenfederatie Nederland, PFN) and medical special-

ists. All DAs are approved by the Dutch Foundation of Easy Reading, who judged that the content is understandable for most people.

The clinical content of the DAs directly reflects current Dutch evidence-based guidelines on the treatment of inguinal hernia, gallstones, knee- or hip osteoarthritis. (2, 3, 29, 30)

The DAs consist of four steps:

1. Information about the condition and treatment options (surgery versus wait and see).
2. A table which displays benefits, harms and probabilities of outcomes of treatment options, plus a knowledge questionnaire to remind about the most important information.
3. Value clarification exercises which help the patient to clarify what matters most to them to decide on a treatment preference.
4. Reflection on responses and indicating treatment preference.

The layout of the DAs is displayed in Figure 3.

Step three and four of the online DA contain a survey to assess the following information: patient's values, patient's treatment preference, and certainty about this preference. The patient's values which are assessed are: concerns about surgery, concerns about complications, impact on daily activities, and experienced discomfort and pain due to the condition. Patients report their preference and their values on a slider ranging from -5 to 5, as illustrated in Figure 3. A score of -5 reflects the preference for watchful waiting, and a score of 5 reflects the preference for surgery. A patient's certainty about their treatment preference is surveyed with a similar slider, ranging from 0-10.

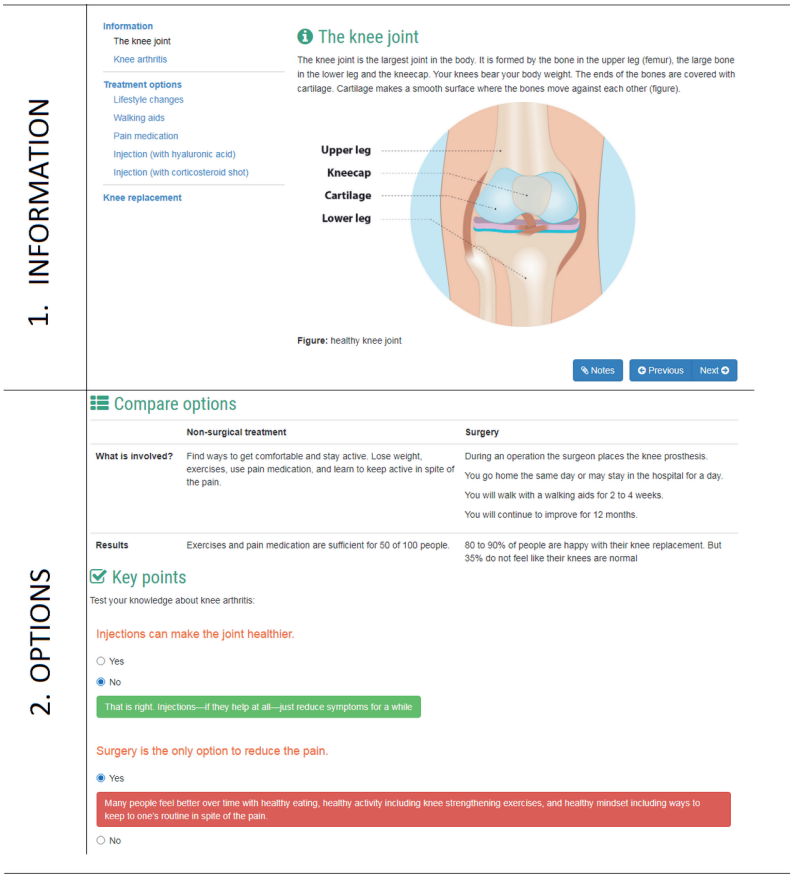
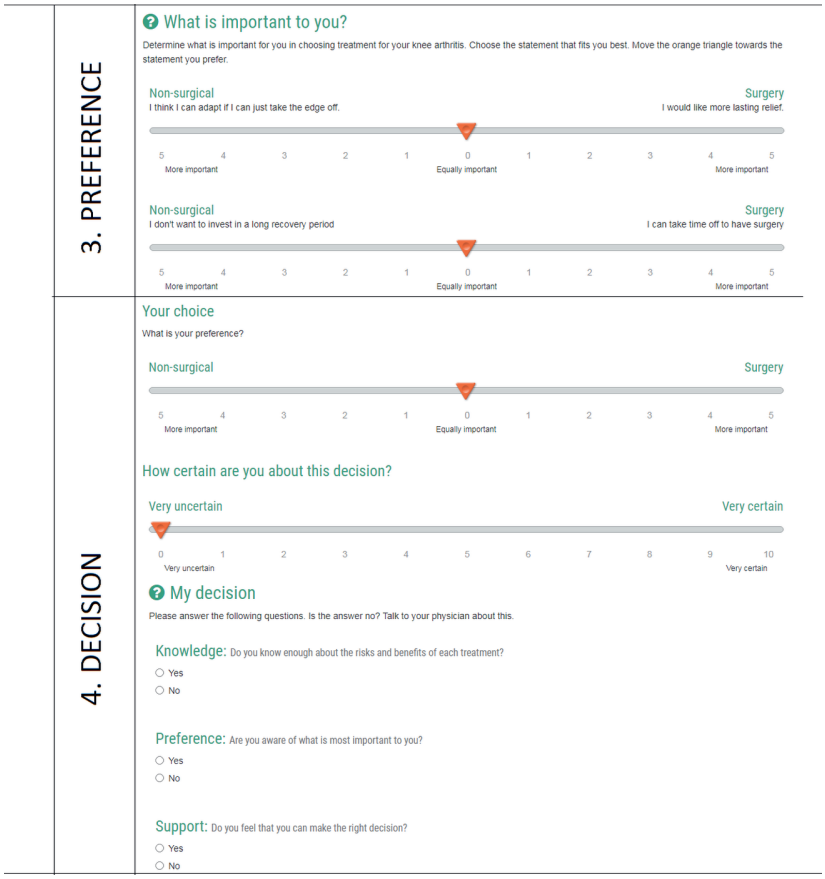


Figure 3. Summarized example of the DA for knee osteoarthritis, with the four corresponding steps


3. PREFERENCE
What is important to you?
Determine what is important for you in choosing treatment for your knee arthritis. Choose the statement that fits you best. Move the orange triangle towards the statement you prefer.
Non-surgical
I think I can adapt if I can just take the edge off.
Surgery
I would like more lasting relief.
5 4 3 2 1 0 1 2 3 4 5
More important
Equally important
More important
Non-surgical
I don't want to invest in a long recovery period
Surgery
I can take time off to have surgery
5 4 3 2 1 0 1 2 3 4 5
More important
Equally important
More important
4. DECISION
Your choice
What is your preference?
Non-surgical
Surgery
5 4 3 2 1 0 1 2 3 4 5
More important
Equally important
More important
How certain are you about this decision?
Very uncertain
Very certain
0 1 2 3 4 5 6 7 8 9 10
Very uncertain
Very certain
My decision
Please answer the following questions. Is the answer no? Talk to your physician about this.
Knowledge: Do you know enough about the risks and benefits of each treatment?
Yes
No
Preference: Are you aware of what is most important to you?
Yes
No
Support: Do you feel that you can make the right decision?
Yes
No

Implementation

Implementation of the SDM strategy is in accordance with a standardized protocol, which consists of four steps: 1) Preparation, 2) Instruction, 3) Implementation of the DA and 4) Evaluation.

During preparation, a local project group is assigned, including a physician, nurse practitioner, front- and back-office support, representative of the communication- and quality control department and the local project leader of the study. The group is responsible for setting goals, defining key results and identifying the clinical pathway of patients.

The instruction consists of 3 workshops for healthcare providers and desk employees to inform about SDM and to give instruction on the use of the DAs.

Implementation of the online DA executed by the local project group under supervision of the project leader of the study.

During evaluation, all stakeholders from the participating department are asked about their experiences with the SDM strategy.

Implementation at different departments will be performed after time intervals of three months and within a time window of two weeks. After 18 months, all departments will work according to the SDM strategy, patient inclusion will continue for another six months. For an overview of the stepped-wedge design and implementation scheme, see Figure 1.

Data collection

The primary outcome, the surgery rates within six months after first presentation at the outpatient clinic, will be retrieved from the Electronic Medical Record (EMR) system of each hospital. Secondary outcomes will be retrieved from the EMR system, online questionnaires, and the patient-reported information assessed by the online DA.

EMRs will be used to extract treatment choice (surgery or conservative treatment) and patient characteristics (gender, age, weight, and height). Questionnaires will be administered online to assess secondary outcomes. All eligible patients will be asked to fill-out these questionnaires at three timepoints: before consultation in which treatment decision is made (baseline), and three and six months after baseline. Informed consent will be obtained before first questionnaire and to avoid contamination, the first questionnaire will be filled out before patients access the DA during the intervention phase.

A detailed overview of the questionnaires is summarized in Table 2. Briefly, the following questionnaires will be used: The CollaboRATE to assess the quality of the decision-making process from the patient perspective (31), the EuroQol-5D-5L (EQ-5D-5L) for generic

quality of life (32), the EuraHS for patients with an inguinal hernia (33), the Gallstone Symptom list (GSL) for patients with gallstones (34), the Knee injury and Osteoarthritis Outcome Score – Physical function Short form (KOOS-PS) for patients with knee osteoarthritis (35), the Hip disability and Osteoarthritis Outcome Score – Physical function Short form (HOOS-PS) for patients with hip osteoarthritis (36), and the Short Form – Health and Labour Questionnaire (SF-HLQ) for the consequences of health problems. (37) Questionnaires will be provided online. After one week, patients will receive reminders by email up to three times to complete the questionnaires.

Table 2. Overview of questionnaire

Questionnaire	Outcome measure	Details	Baseline	3 months	6 months
CollaboRATE (31)	Level of SDM	A 3-item questionnaire measuring the experienced level of SDM.	-	x	-
EuroQol-5D-5L (EQ-5D-5L) (32)	Quality of life	A 6-item questionnaire across 5 domains: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems. The questionnaire is scored with a 1-digit number that expresses the level selected for that dimension. The digits for the five dimensions can be combined into a 5-digit number that describes the patient's health state. The last question is a VAS-score (range: 0-100) representing the patient's self-rated health with 100 being 'The best health you can imagine' and 0 being 'The worst health you can imagine'.	x	x	x
Gallstone Symptom List (GSL) (34)	Disease related Complaints	A 6-item questionnaire. This specific pain score was designed and previously used in a large cohort of patients in the United Kingdom. This questionnaire was designed to asses symptoms associated with symptomatic cholecystolithiasis.	x[a]	x[a]	x[a]
EuraHS (33)	Disease related Complaints	A 9-item questionnaire across 3 domains: pain, restriction of activities, and cosmetic discomfort. The questionnaire is scored on an 11-point scale from 0-10, total score ranges from 0-90 with low scores being favourable outcomes.	x[a]	x[a]	x[a]
Knee injury and Osteoarthritis Outcome Score (KOOS-PS) (35)	Disease related Complaints	A 7-item questionnaire about physical functioning of patients with knee complaints, experienced in the last week. The questionnaire is scored on a 5-points Likert scale (0-4) where 0 is no difficulty experienced and 4 is extreme difficulty.	x[a]	x[a]	x[a]

Questionnaire	Outcome measure	Details	Baseline	3 months	6 months
Hip disability and Osteoarthritis Outcome Score (HOOS-PS) (36)	Disease related Complaints	A 5-item questionnaire about physical functioning of patients with hip complaints, experienced in the last week. The questionnaire is scored on a 5-points Likert scale (0-4) where 0 is no difficulty experienced and 4 is extreme difficulty.	x[a]	x[a]	x[a]
Short Form Health and Labour Questionnaire (SF-HLQ) (37)	Consequences on employment	This questionnaire concerns the consequences of health problems for employment in a paid job and for unpaid work (e.g. household chores). These questions pertain to the period covering the past month. Health problems refer both to your physical and emotional problems.	x	x	x

[a] Patients only receive one of these questionnaires per timepoint, depending on patient's condition

Sample size

Sample size calculations are based on differences in operation rate before and after the introduction of SDM. The sample size calculation is based on the formulas for a stepped-wedge design as proposed by Woertman et al. (38) Based on existing literature, the following reduction in surgery rate per condition is assumed: 10% for inguinal hernia, 10% gallstone disease, 5% for knee osteoarthritis, and 7% for hip osteoarthritis. (39-43)

With the assumptions of a ß of 0.8, an a of 0.05 (two-sided) and an intraclass correlation of 0.10, the estimated sample sizes for inguinal hernia, gallstone disease, knee- and hip osteoarthritis are 50, 45, 120, and 95 patients per department per three months, respectively. Total estimated sample sizes for inguinal hernia, gallstone disease, knee- and hip osteoarthritis are 2400, 2160, 5760, and 4560 patients, respectively.

Effect evaluation

Surgery rates will be calculated at department level each 3-month period and evaluated over time. Comparisons of surgery rates will be made before and after implementation of the SDM strategy. Secondary outcomes will be compared between patients included before and after implementation of the SDM strategy.

Cost-effectiveness

The economic evaluation will be undertaken alongside the clinical study, as cost-effectiveness analysis (CEA) with the costs per patient at six months follow-up. Additionally, a cost-utility analysis (CUA) will be performed with the costs per quality-adjusted life-year (QALY) as outcome. Both analyses will be performed from a societal perspective, and the time horizon is set at six months.

Both direct and indirect medical costs will be considered. These direct and indirect medical costs include: costs of inpatient and outpatient hospital stay, major diagnostic and therapeutic procedures, consultations, costs of out-of-hospital care by general practitioner and allied healthcare providers, non-medical out-of-pocket expenses (over-the-counter medication, informal care), and indirect non-medical costs of production loss from sick leave. These costs will be determined with data from the EMR and with data from questionnaires. The EQ-5D-5L questionnaire will be used at different timepoints to generate health status scoring profiles over time, which will be transposed into health utilities using country specific population-based tariffs of time trade-off ratings of health states.

Process evaluation

In a process evaluation we will assess facilitators and barriers that influence the implementation process and adoption of the SDM strategy, making use of existing frameworks for the implementation of SDM. (44-46) This evaluation will also yield more in-depth information about relevant contextual factors and experiences of patients and healthcare providers (i.e. physicians and nurses) with the SDM strategy in general and with the DAs more specific. For this purpose, we will organize focus groups with patients and healthcare providers.

Statistical Methods

Baseline characteristics will be described using descriptive statistics. If continuous, Student's t-test will be used to calculate differences between clusters for normally distributed data. Mann-Whitney U-test will be used for skewed data.

Mixed models will be used to analyse the data from the stepped-wedge design and to account for clustering of patients within hospitals at different follow-up periods. We will analyse the effect of the intervention in comparison with usual care on the primary outcome surgery rates. We will adjust for confounding factors, such as age, sex, clinical parameters (e.g. comorbidity), and working and social activities. Furthermore, we will use mixed models to analyse the effect of the SDM strategy regarding the secondary outcomes and to account for clustering of repeated measurements within patients and clusters of patients within hospitals. In addition, we will include time as a covariate in order to investigate time trends. When applicable, we will test assumptions of normality and linearity, and interaction terms.

Safety monitoring and data access

Data will be captured and stored in an online registry (Castor EDC) during the control phase. During intervention phase, answers to questionnaires and in DAs will be stored in a second secured environment, which is password protected and can only be accessed by investigators. All data will be stored pseudonymized. Locking of data and code list will take place after the end of follow-up of the last included patient, and data will be stored for 15 years. Data management will be performed in accordance with FAIR guiding principles. (47)

Ethical consideration

The protocol of the study was registered under file number 2018-4815 and assessed by the Central Committee on Research Involving Human Subjects of Arnhem-Nijmegen (CCMO Arnhem-Nijmegen). The committee confirmed the Medical Research Involving

Human Subjects Act (WMO) does not apply. Local ethics assessment committees of the participating hospitals are requested to approve the protocol as well.

DISCUSSION

The results of the E-valuAID will clarify if the implementation of an SDM strategy with online DAs in surgical- and orthopaedic practices reduces surgery rates and is cost-effective compared to usual care. This multicentre study with a stepped-wedge design will show the effect of an SDM strategy on surgery rates, patient-reported outcomes, and cost-effectiveness. We hypothesize that the application of DAs will result in lower surgery rates, while improving patient-reported outcomes.

Rationale of the study design

In the present study we chose a pragmatic approach to investigate the effectiveness of SDM with an online DA. A recent systematic review shows that the stepped-wedge design is particularly used for practical and methodological purposes, which makes it well-suited for this study. (48) For example, as only a limited number of clinics start simultaneously, this design allows a thorough implementation of the intervention in each clinic. The implementation protocol requires a dedicated introduction of SDM to the users by providing information about the study and the online DA. Moreover, the design allows for evaluation of both the effect on surgery rates on a hospital level and outcomes on a patient level. An alternative design of a randomized trial on patient-level would have the potential pitfall of contamination of usual care by the intervention strategy, as it is conceivable that specialists transfer their SDM experience and methods to usual care. Cluster randomization of departments appeared not feasible during the explorative discussions with participating hospitals. They strongly preferred to start the implementation of the SDM strategy at a predetermined moment in time, and our logistic inability to implement randomly decided to refrain from cluster randomization. In the present design, the potential risk of selection bias, due to clinicians' decision of not providing an SDM strategy is negligible, as all consecutive patients receive a DA before their first consultation.

Current evidence for SDM in surgery

Although the effect of SDM and provision of DAs on patient satisfaction are promising (49, 50), there is a knowledge gap on the impact of SDM-instruments in terms of cost-effectiveness. Up to date, no trials are performed to evaluate the cost-effectiveness of DAs in patients with an inguinal hernia or gallstones. One study evaluated the impact of a DA consisting of a 50 minute video and a booklet in 343 patients with knee- or hip osteo-

arthritis. This RCT showed DAs were cost-effective, with similar health outcomes. (51) Furthermore, Stacey et al. reviewed the literature in 2017, and they included four trials with 570 patients with knee or hip osteoarthritis. (40, 41, 52, 53) These studies assessed various effects of a DA: patient knowledge, the efficiency of decision-making, or wait times between screening and definitive choice, but not on cost-effectiveness. Only our retrospective evaluation on the effect of online DAs in patients with an inguinal hernia or cholecystolithiasis suggested a reduction in surgical interventions, but a cost-effectiveness analysis was lacking. (39) In the absence of existing evidence, it is clear that more knowledge on the benefits of SDM from patient and societal perspectives is necessary. The E-valuAID aims to solve the current void in the literature on the benefits of SDM and online DAs. Results of the present study as proposed here, will affect healthcare policy concerning decision-making in surgery for the coming decades.

In conclusion, SDM is eminently applicable in patients with an inguinal hernia, gallstones, knee- or hip osteoarthritis due to both a surgical and conservative treatment option. This study will show whether an SDM-strategy will lead to a reduced surgery rate and if future implementation is cost-effective.

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CHAPTER

10

The association between patients' preferred treatment after the use of a patient decision aid and their choice of eventual treatment

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Health expectations 2020



ABSTRACT

OBJECTIVE To investigate the association between patients' preferred treatment and eventual treatment. Second, to compare patients with surgical treatment to watchful-waiting in order to identify predictive factors for surgery.

METHODS A single-center retrospective study was performed between December 2015 and August 2018. Patients (≥18 years) who used a patient decision aid (PDA) for gallstones or inguinal hernia were included. After their first surgical consultation, patients received access to an online-PDA. The patients' preferred treatment after the PDA was compared with their choice of eventual treatment. Multivariable regression analyses were performed for predictive factors for surgery.

RESULTS In total, 567 patients with gallstones and 585 patients with an inguinal hernia were included. Of the patients with gallstones, 121(21%) preferred watchful waiting, 367(65%) preferred surgery, and 79(14%) were not sure. The patients' preferred treatment was performed in 85.9%. Frequent pain attacks (OR2.1, 95%CI 1.1-3.9, p=0.020) and preference for surgery (OR4.4, 95%CI 1.9-10.1, p=0.001) independently predicted surgery.

Of the patients with an inguinal hernia, 77(13.2%) preferred watchful waiting, 452(78.8%) preferred surgery, and 56(9.6%) were not sure. The patients' preferred treatment was performed in 86.0%. The preference for surgery (OR5.2, 95%CI 2.5-10.6, p<0.001) independently predicted surgery and worry about complications predicted avoidance of surgery (OR0.5, 95%CI 0.2-1.0, p=0.037).

CONCLUSION This study, reflecting current clinical care, shows that patients' preferred treatment after using a PDA matches their eventual treatment choice in 86% of patients with gallstones or an inguinal hernia. In these patients, symptoms and patients' preference for surgery independently predicts eventual choice of surgery.

INTRODUCTION

An increasing number of patients want to be involved when a decision needs to be made between treatment options, commonly called shared decision making (SDM). (1) As time is a limiting factor for SDM in the consulting room, SDM is frequently facilitated by (online) patient decision aids (PDAs). PDAs present comparative information about advantages and disadvantages of available options and evaluate personal values and preferences of the patient. (2-4)

PDAs are proven to be effective in improving knowledge, reducing decisional conflict and moreover, changing patients' preferred treatment. (5) Our group recently showed that PDAs reduce operation rates in patients with gallstones or an inguinal hernia. (6) This change may be caused by the impact of the PDA on patients' preferences and cause a decision shift. (7) Patients' preference on treatment is influenced by several factors. First, the preference is influenced by the patients' symptoms and their concern about the course of the condition. Second, the physician's advice is important in development of patients' preferred treatment. (8-10) Third, treatment options, risks associated with each option, and expectations of results can influence patients' preference. (7, 11, 12) A PDA additionally informs a patient on treatment options and associated risks, but also explores patients' values to determine what is most important for the individual patient. Current PDAs consist of a personal value clarification exercise, which helps patients to identify their own values and find the treatment option most consistent with their preference. However, it is unknown which personal values are important in the preference for surgery. (13) Knowledge concerning factors influencing patients' preferences and treatment decisions are important to improve SDM. (14)

Gallbladder surgery and hernia repair are both, to a degree, considered to be examples of preference sensitive care. (15) International guidelines support watchful waiting in selected patients if symptoms are mild and the condition does not show signs of potential complications. (16-18) Cholecystitis or biliary pancreatitis are potential complications of gallstones, while in case of an inguinal hernia a complicated course may result in a bowel incarceration. Nevertheless a non-operative treatment is important to consider, especially since it is known that cholecystectomy is a sub-optimal solution to treat pain in patients with gallstones and abdominal symptoms and the long term outcomes of hernia repair are variable. (19-21) These variations in outcomes make it essential that patients are invited to participate in treatment decisions based on information about potential complications, surgical morbidity or the outcome after conservative management.

Current research mostly focuses on the patients' preferences, but information about the association between preferences and their choice of eventual treatment is not yet

reported. (7) Therefore, the aim of this study was to investigate the association between the preferred treatment option after PDA usage and the eventual choice of treatment. Secondly, we identified clinical factors and patient values that predicted a decision to have surgery.

METHODS

Study design & study population

A single center retrospective study was performed in a community hospital in the Netherlands. Patients were eligible for participation in the study if they were ≥ 18 years of age and used a PDA between December 2015 and August 2018. All patients with an emergency indication for surgery were excluded.

PDAs for patients with gallstones or an inguinal hernia were integrated into the standard workflow at the surgical outpatient clinic in December 2015. Physicians were trained in SDM to support the implementation of PDAs. This training covered the use of the PDA with a patient. Moreover, a workgroup was formed, consisting of at least: a medical doctor, a project manager (from the hospital), a nurse of the outpatient clinic and a department manager of the outpatient clinic. Objectives for the use of the PDAs were set, as well as the care process for patients. Workshops were organized to inspire about SDM, to explain how the PDAs work and to train communication skills to empower patients to participate in the decision making process, assess patients' preferences and health values.

In the Netherlands, patients are referred to the surgical outpatient clinic by their general practitioner after the diagnosis of symptomatic gallstones or after the diagnosis of an inguinal hernia, based on ultrasound imaging in the local hospital if applicable. (16) During the first consultation in the outpatient clinic, the surgeon takes the history, performs physical examination and counsels patients. The condition and choices in treatment, including conservative treatment are explained. The risks of treatments are discussed after which, a PDA is introduced. A new appointment is made after 1-2 weeks ensuring careful decision-making and informed consent. During the second appointment the results of the PDA are discussed with the patient and treatment choice is made using a SDM approach (Figure 1).

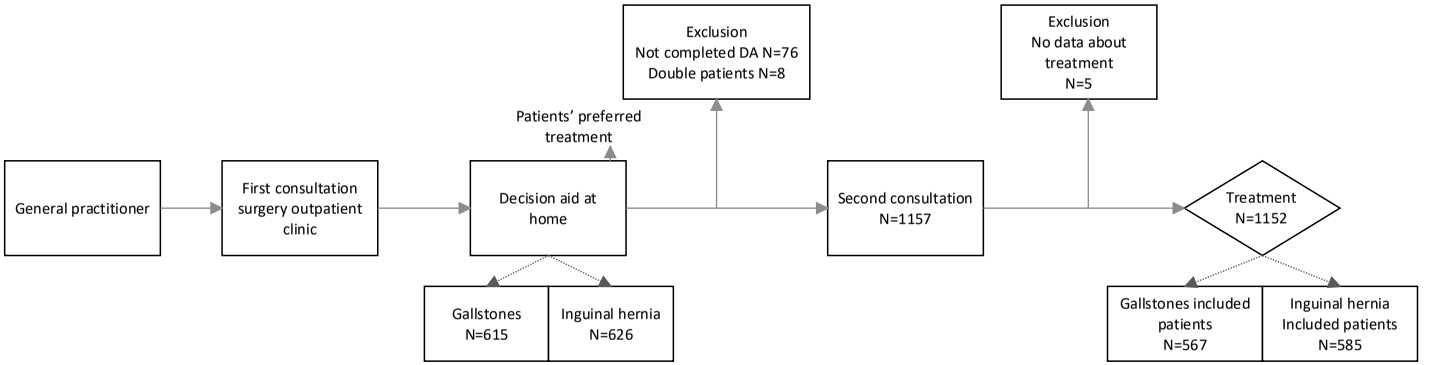

Figure 1. Flow chart of surgical consultations, decision aid and inclusion of patients. Flow chart of surgical consultations and the timing of the online decision aid and measurement of patients' preferred treatment. This flow chart also shows the inclusion of patients. 615 patients with gallstones used the decision aid and eventually 567 patients were included. Between December 2015 and August 2018 626 patients with an inguinal hernia used the decision aid and eventually 585 patients were included

The local medical ethical committee and the boards of directors approved the study protocol (registration number 2018-4587). This research was performed in accordance with the ethical standards of the updated Helsinki Declaration of 2013. The results are presented according to the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines. (22)

Patient decision aids

The online PDAs (https://www.decisionaid.info) were developed by patients and physicians according to the International Patient Decision Aids Standards (IPDAS) (http://ipdas.ohri.ca/). Surgery and watchful waiting are compared in five steps (Supplementary file 1 and 2). Detailed information about the five steps of the PDAs have been described elsewhere. (6)

Outcome & data collection

To obtain information about the association between preference and eventual choice of treatment after PDAs, we compared the patients' preferred treatment after PDA and their eventual choice of treatment. The outcome of this study is the percentage of patients in which the patients' preferred treatment matched their eventual choice of treatment. Secondary outcomes were: certainty about their preferred treatment and predictive factors (patient characteristics, patients' preference, disease burden and personal values) for surgery.

Data about patients' preferred treatment, certainty about their preference, disease burden, and personal values were derived from the PDA. Questions about disease burden and personal values were presented as two statements on each side of a slider (ranging from -5 to 5). For every statement, the left side represented watchful waiting and the right side represented surgery. Patients moved the triangle to the side they agreed most with. Patients with gallstones specified their disease burden and personal values about *frequency of pain attacks, complaints,* and *concerns about surgery*. Patients with an inguinal hernia specified their disease burden and personal values about *discomfort, concerns about surgery, bowel incarceration,* and *surgical complications.* The patients were asked to point out their preferred treatment choice, on a slider ranging from -5 (watchful waiting) to 5 (surgery). Last, patients indicated how certain they were with their preferred option on a slider, ranging from 0 to 10. Age, sex, and their eventual choice of treatment were derived from the hospital register in January 2018.

Statistical analysis

Patients who had not completed the PDA, whose data about their eventual choice of treatment were not available from the hospital register, and patients who had com-

pleted multiple PDAs for the same condition were excluded from the analysis. The data of patients with gallstones and inguinal hernia were analyzed and presented separately.

The patients' preferred treatment, originally scored on an eleven-point scale from -5 to 5, was first transformed into a categorical scale. Scores of -5 to -2 represented the preference watchful waiting; -1 to 1 represented not sure and 2 to 5 represented surgery. The sensitivity of this transformation was tested by also applying an alternative transformation: -5 to -3 represented watchful waiting; -2 to 2 represented not sure/intermediate and 3 to 5 represented surgery (no differences with main outcome, data not shown). The value clarification exercise also consisted of eleven-point scales from -5 to 5; these were transformed with the same cut-off scores.

Categorical data (sex, patients' preferred treatment, their eventual choice of treatment, disease burden, and personal values from the value clarification exercise) were summarized by frequencies and proportions. Continuous data (age, certainty) were presented as mean ± standard deviation (SD) when normally distributed and median with range or inter quartile range (IQR) when non-normally distributed. To investigate the association between patients' preferred treatment and their eventual choice of treatment, a bar chart with both variables was presented.

Patients were compared based on their eventual choice of treatment (watchful waiting and surgical) by age, sex, disease burden, personal values, and their preferred treatment. Comparison of these variables was done using chi-squared test for dichotomous data, Student's t-test for normally distributed continuous data and the Mann-Whitney U test for skewed continuous data. Testing for normality of data distributions was based on the Shapiro-Wilks test.

To identify predictive factors for performing surgery, first univariate logistic regression analyses were performed with their eventual choice of treatment (watchful waiting/surgery) as dependent variable and patients' preferred treatment (watchful waiting, not sure and surgery), age, sex, disease burden and personal values, as independent variables. These were all included in the multivariable model. The outcomes of the univariable and multivariable analyses were presented as an Odds Ratio (OR) and 95% confidence interval (CI).

Associations with a p-value less than 0.05 were considered statistically significant. All missing values were considered to be at random and were excluded from analyses. Analyses were performed using SPSS statistics version 25.0 (IBM).

RESULTS

Patients

Between December 2015 and August 2018 1,075 patients were referred to the surgical outpatient clinic with symptomatic gallstones and 1,219 patients with an inguinal hernia. PDAs were used by 615 patients (74.5%) with gallstones and 626 patients (76.1%) with an inguinal hernia. In addition, 89 patients (7.2%) were excluded from analyses, because patients had not finished the PDA, no data were available about eventual choice of treatment, or patients had completed multiple PDAs (Figure 1).

In total, 567 patients with gallstones (median age 52 years IQR 41-63, 30.0% male) and 585 patients with an inguinal hernia (median age 60 years, IQR 49.5-70.5, 92.1% male) were eligible for analysis. Baseline characteristics are described in Table 1.

Table 1 - Characteristics and treatment of included patients

	Gallstones (n=567)	**Inguinal hernia (n=585)**
Age, years (median, IQR)	52 (41-63)	60 (49.5-70.5)
Sex, (M:F, %M)	170:396(30.0)	539:46 (92.1)
Patients' treatment preference		
Watchful waiting (n, %)	121 (21.3)	77 (13.2)
Not sure (n, %)	79 (13.9)	56 (9.6)
Surgery (n, %)	367 (64.7)	452 (78.8)
Eventual choice of treatment		
Watchful waiting (n, %)	172 (30.3)	147 (25.1)
Surgery (n, %)	395 (69.7)	438 (74.9)

Patients' preferred versus eventual choice of treatment

The patients' preferred treatment was their eventual choice of treatment in 85.9% of patients with gallstones. In patients with an inguinal hernia, the patients' preferred treatment was their eventual choice of treatment in 86.0%. In both groups, 14% of patients were not treated according to their preference reported in the DA.

Of the patients with gallstones, 121 (21.3%) preferred watchful waiting at the end of the DA, 79 (13.9%) were not sure, and 367 (64.7%) preferred surgery (Table 1). In total, 395 patients (69.7%) underwent a gallbladder removal. Figure 2a shows the association between the patients' preferred treatment at the end of the PDA and their eventual choice of treatment.

Of the patients with an inguinal hernia, 77 (13.2%) preferred watchful waiting, 56 of

patients (9.6%) were not sure, and 452 (78.8%) preferred surgery. In total, 147 patients (25.1%) were treated conservatively and 438 patients (74.9%) had surgery. Figure 2b shows the association between the patients' preferred treatment at the end of the PDA and their eventual choice of treatment.

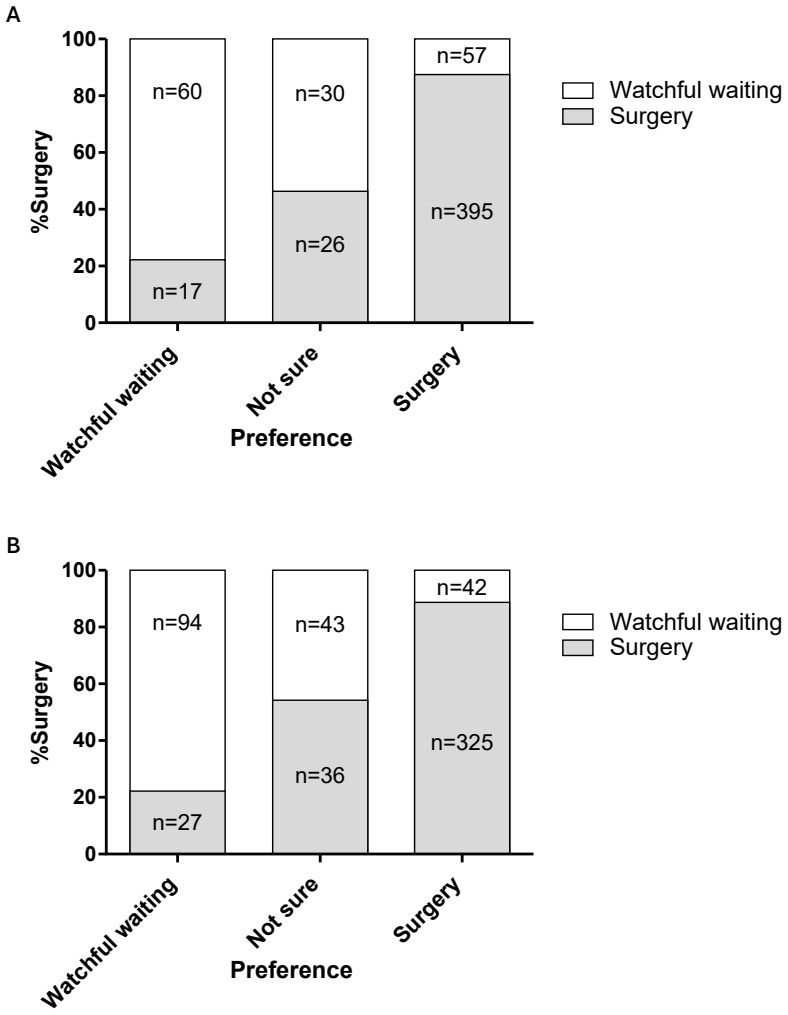

Figure 2. A, Gallstones—Eventual choice of treatment in patients with the preference watchful waiting, not sure and surgery. B, Inguinal hernia—Eventual choice of treatment in patients with the preference watchful waiting, not sure and surgery. Patients are divided by their preferred treatment. On the y-axis, the percentage of eventually chosen surgeries is shown. The grey parts of the columns represent surgery, and the white parts represent watchful waiting

Certainty about preferred treatment

For both conditions, patients who preferred surgery were more certain about their preference compared to patients who preferred watchful waiting. In patients with gallstones median scores were 9.0 (IQR 8.0-10.0) and 7.0 (IQR 5.5-8.5) respectively for the prefer-

ence surgery and watchful waiting (p<0.001). In patients with an inguinal hernia median scores were 9.0 (IQR 8.0-10.0) and 8.0 (IQR 7.0-9.0) respectively for surgery and watchful waiting (p<0.001).

Predictive factors for surgery

In table 2 and 3 patients with a surgery were compared with patients who underwent a watchful waiting strategy. Patients with gallstones who underwent surgery were younger compared to patients who waited (50.1 ± 15.1 versus 55.6 ± 14.9, p<0.001). Surgical patients were characterized by reporting more pain attacks, major complaints, and less concern about surgery compared to patients with a watchful waiting policy (p <0.001 for each comparison). In multivariable analyses, only frequent pain attacks (OR 2.1, 95% CI 1.1-3.9, p=0.020) and preference for surgery (OR 4.4, 95% CI 1.9-10.1, p=0.001) were independently predictive factors for surgery.

Table 2 – Characteristics, disease burden, personal values and treatment preference of patients with gallstones with watchful waiting (n=172) and surgery (n=395).

	Watchful waiting (n= 172)	Surgery (n= 395)	p-value	Univariable Odds Ratio (95%CI)	Multivariable Odds Ratio (95%CI)
Sex, male	47 (27.3)	123 (31.1)	0.353	1.207 (0.811-1.796)	1.425 (0.844-2.406)
Age, years (median, IQR)†	56.0 (45.5-66.5)	50.0 (38-62)	<0.001	**0.967 (0.964-0.988)**	0.992 (0.976-1.008)
Pain attacks			<0.001		
Infrequent pain attacks	74 (43.0)	42 (10.6)		**0.467 (0.268-0.816)**	1.394 (0.656-2.960)
Intermediate	42 (24.4)	51 (12.9)		1	1
Frequent pain attacks	56 (32.6)	302 (76.6)		**4.441 (2.699-7.308)**	**2.118 (1.135-3.952)**
Complaints			<0.001		
Minor complaints	99 (57.6)	39 (9.9)		**0.210 (0.114 -0.386)**	0.565 (0.247-1.295)
Intermediate	25 (14.5)	47 (11.9)		1	1
Major complaints	48 (27.9)	309 (78.2)		**3.424 (1.931-6.071)**	0.903 (0.377-2.164)
Worry about surgery			<0.001		
Worried	83 (48.2)	76 (19.2)		**0.364 (0.214-0.619)**	0.561 (0.284-1.105)
Intermediate	29 (16.9)	73 (18.5)		1	1
Not worried	60 (34.9)	246 (62.3)		1.629 (0.974-2.725)	0.814 (0.421-1.575)
Treatment preference			<0.001		
Watchful waiting	94 (54.7)	27 (6.8)		**0.240 (0.130-0.445)**	0.339 (0.163-0.707)
Not sure	36 (22.7)	43 (10.9)		1	1
Surgery	42 (24.4)	325 (82.3)		6.647 (3.749-11.20)	4.148 (1.791-9.604)

Univariable and multivariable scores in bold have a p-value < 0.05. †Analyzed with Mann-Whitney U-test.

In patients with an inguinal hernia similar outcomes were found. Surgically treated patients were younger compared to patients who waited (56.8 ± 14.4 versus 61.1 ± 14.4, p=0.002). Surgical patients were characterized by more discomfort, less concern about surgery, less concern about risks of surgery, and more concern about bowel incarceration, compared to patients with watchful waiting (p<0.001 for all comparisons). In multivariable analyses, the preference for surgery (OR 5.2, 95% CI 2.5-10.6, p<0.001) independently predicted surgery and worry about complications of surgery was negatively associated with surgery (OR 0.5, 95%CI 0.2-1.0, p=0.037).

Table 3. Patient characteristics, disease burden, personal values and treatment preference of patients an inguinal hernia with watchful waiting (n=147) and surgery (n=438).

	Watchful waiting (n= 147)	Surgery (n= 438)	p-value	Univariable	Multivariable
Sex, male (n, %)	131 (89.1)	408 (93.2)	0.116	1.661 (0.878-3.143)	1.515 (0.657-3.492)
Age, years (median, IQR)†	63.0 (53-73)	58.0 (48-68)	0.002	**0.978 (0.965-0.992)**	0.991 (0.975-1.008)
Discomfort			<0.001		
Little discomfort	83 (56.5)	64 (14.6)		**0.274 (0.512-0.491)**	0.671 (0.320-1.408)
Intermediate	22 (15.0)	62 (14.1)		1	1
Much discomfort	42 (28.6)	312 (71.2)		**2.636 (1.471-4.724)**	1.879 (0.967-3.651)
Worry about surgery			<0.001		
Worried	34 (23.1)	37 (8.4)		0.544 (0.293-1.009)	0.691(0.300-1.595)
Intermediate	35 (23.8)	70 (16.0)		1	1
Not worried	78 (53.1)	331 (75.6)		**2.122 (1.320-3.411)**	1.167 (0.591-2.305)
Worry about incarceration			<0.001		
Not worried	63 (42.8)	73 (16.7)		**0.338 (0.205-0.555)**	0.691 (0.347-1.375)
Intermediate	37 (25.2)	127 (29.0)		1	1
Worried	47 (32.0)	238 (54.3)		1.475 (0.911-2.388)	0.770 (0.413-1.435)
Worry about complications of surgery			<0.001		
Worried	42 (28.6)	40 (9.1)		**0.306 (0.173-0.542)**	**0.467 (0.223-0.975)**
Intermediate	37 (25.2)	115 (26.3)		1	1
Not worried	68 (46.3)	283 (64.6)		1.339 (0.848-2.111)	0.936 (0.501-1.748)
Treatment preference			<0.001		
Watchful waiting	60 (40.8)	17 (3.9)		**0.327 (0.154-0.694)**	0.589 (0.243-1.428)
Not sure	30 (20.4)	26 (5.9)		1	1
Surgery	57 (38.8)	395 (90.2)		**7.996 (4.414-14.48)**	**5.158 (2.508-10.61)**

Univariable and multivariable scores in bold have a p-value < 0.05.

DISCUSSION

The present study, reflecting real life clinical decision making, shows that general surgical patients' preference for either watchful waiting or surgery after a PDA is highly associated with their eventual choice of treatment. Patients who prefer surgery seem to be more certain about their preference compared to patients who prefer watchful waiting. In patients with gallstones, 'frequent pain attacks' is an independent predictive factor for surgical treatment. In both patient groups, with gallstones or inguinal hernia, the patients' preference for surgery is an independent predictive factor for surgical treatment. In patients with an inguinal hernia, 'worry about complications of surgery' is associated with avoidance of surgery. Fourteen percent of patients are not treated according to their preference reported in the DA.

The majority of patients with gallstones or inguinal hernia prefer surgery after using a PDA. It could well be that patients' preference for surgery contributes to the nationwide operation rates in the Netherlands above 70% for both conditions. (19) Despite the finding that watchful waiting is a good alternative in selected patients with symptomatic gallstones or an inguinal hernia(16, 23, 24), it looks like most patients prefer a quick and definitive solution for their symptoms. (25-28) That is in line with our finding that the majority of surgical patients report that they are very certain about their preference. This might be explained by the patients' anticipation on a surgical treatment after their general practitioner explained the potential cause of their symptoms and an ultrasound confirmed the diagnosis of gallstones or an inguinal hernia. SDM is in case of preference sensitive care even more important; counseling patients and create awareness of potential disadvantages of surgery is mandatory.

The way PDAs should be provided and integrated into the workflow is debated. Different PDA formats are available (booklet, audio, online), interactive or not, and PDAs can be provided at different locations or time points (at general practitioner, before surgical consultation, after first surgical consultation). (29) In the present study, the online link to the PDAs was provided after the first consultation with the patients' surgeon. During the second consultation the eventual choice of treatment was chosen. Alternatively, the PDA could be provided by the general practitioner, before referral to the surgeon. Implementation of PDAs and SDM earlier in the clinical pathway leads to the following advantages; improved patient knowledge, patients who are more clear about their values, reduced decisional conflict, and potential; fewer referrals, reduced diagnostics, and less invasive treatments. (5, 30) Moreover, general practitioners are probably more aware of the patients' values due to a long-lasting relationship and considerations and can alter expectations in a timely fashion. (31)

The discrepancy between patients' initially preferred treatment and different eventual

choice of treatment is of interest. This study shows a discrepancy in 14% of patients with gallstones or inguinal hernia. This could reflect the surgeons' opinion who advised a different treatment, patients could have shifted their preference after usage of the PDA for example in conversation with family or friends, or the condition could have presented with signs of a potential complicated course (e.g. cholecystitis or bowel incarceration). It is of interest that patients who initially preferred watchful waiting less often received their preferred treatment compared to patients preferring surgery (77.8% versus 87.9%). Due to the retrospective aspect of this study, we were unable to analyze the potential causes of this phenomenon further.

This is the first study that shows the association between patients' preferred treatment, expressed after using a PDA, and their eventual choice of treatment. Strengthening the study is the real-life study design, which shows daily clinical practice compared to ~~a~~ controlled condition within randomized controlled trials. However, this study also comes with limitations. The major limitation of this study is missing information about the consultation with the general practitioner and the first surgical consultation. Available data is obtained from the PDAs, which were provided to patients after these two consultations. Therefore, we cannot assess the exact impact of the PDA on the patients' preferences, as we don't know their initial preferences. Secondly, due to the lack of a control group we are not able to compare outcomes between patients with and without our intervention.

As this study only included patients with gallstones or an inguinal hernia who used a PDA, it remains unclear what happens with preferences of patients who consult their surgeon but do not use PDAs. It could be hypothesized that the discrepancy between the initial patients' preference and their eventual choice of treatment could be greater, because the increase in knowledge concerning treatment options and risks is missing. Finally, our research only assessed patient preferences in surgical candidates and the impact of PDAs in patients with non-surgical conditions is of also of interest.

To overcome the methodological limitations of the present study, we started a prospective assessment (Dutch Trial Register NTR7501). As a result of longitudinal data collection, the influence of disease status, patients' values, preference shifts will clarify more clearly the discrepancy between patients' preferred treatment and their eventual choice of treatment.

To date, surgeons are mainly focused on potentially complicated course of a condition (e.g., cholecystitis and bowel incarceration) or surgical complications (e.g., bile duct injury or persistent pain), while patients are more focused on long term outcomes and working disability. (16, 23, 24, 32) To improve SDM in clinical practice, physicians should be aware of this discrepancy. (33) Furthermore, as our data shows differences between surgically treated and non-surgically treated patient, age and personal values, personal-

ized patient DAs are the next step in improving SDM. The benefits and risks pointed out in the PDA, the option grid, and the value clarification exercises should all be related to the characteristics of patients. Then patients' preference can be better explored, and satisfaction of patients may increase.

In conclusion, patients reported preferred treatment after the use of a PDA is highly predictive for the eventual choice of treatment in patients with gallstones or an inguinal hernia. Fourteen percent of patients with symptomatic gallstones or an inguinal hernia do not undergo preferred treatment. In patients with gallstones, their physical complaints are more predictive for a surgical intervention than their worry about surgery related complications.

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CHAPTER

11

GENERAL DISCUSSION



In this thesis, we sought to improve the diagnostic, therapeutic, and decision-making framework for patients with uncomplicated symptomatic gallstone disease. This objective was addressed in nine chapters structured around three themes. Part I explores the clinical pathway of patients with gallstone disease across both primary and secondary care. It highlights the diagnostic challenges in primary care and that laparoscopic cholecystectomy effectively relieves biliary colic, but also improves several abdominal symptoms commonly attributed to functional disorders, such as bloating and dyspepsia. In Part II, we introduced a novel "textbook outcome" for gallstone disease and developed the Gall-Q, a concise, disease-specific quality-of-life instrument. Part III focuses on shared decision-making in the context of elective surgery, with particular attention to the use of decision aids.

In the following sections, the significance of the studies presented in this thesis will be discussed within three overarching themes: 1) Complexities and uncertainties in gallstone disease 2) outcome assessment in gallstone disease, and 3) the roles of healthcare professionals and patients.

Complexities and uncertainties in gallstone disease

In contrast to complicated gallstone disease (such as biliary pancreatitis, cholangitis, or acute cholecystitis) where cholecystectomy is clearly indicated, considerable uncertainty remains regarding the diagnosis and treatment of patients with uncomplicated gallstone disease. Up to 40% of patients have persistent pain after cholecystectomy. Moreover, a significant proportion of patients with gallstones also meet criteria for irritable bowel syndrome or functional dyspepsia, contributing to overlapping and often ambiguous symptom profiles. (1-3) Watchful waiting is increasingly considered as a viable strategy. Our findings in Chapter 4 and 5 support the premise that most patients with gallstones will not develop complications. For example, Chapter 4 showed an increase in presentations of patients with complicated gallstone disease, but this increase appeared limited to patients who initially presented with complicated gallstone disease. Among patients seen in an outpatient setting with uncomplicated disease, the risk of complications remained low, approximately 2.5% per half year. This finding further supports conservative management for many patients. These data are underlined by previous randomized controlled trials in which the incidence of biliary complications of patients with uncomplicated gallstone disease at the outpatient clinic is 2-6% in one to five years of follow-up. (4-6) Notably, previous research has also shown that approximately half of patients do not experience a preceding "warning" biliary colic before they develop a biliary complication, highlighting the abrupt onset in many cases. (7) These findings support a classification of complicated gallstone disease into two distinct categories: *primary* and *secondary* complicated gallstone disease. The former refers to

patients whose initial presentation of gallstone disease is with complicated gallstone disease. The latter refers to patients who initially present with symptomatic gallstone disease and subsequently develop a complication. Following these terms, patients with gallstones can be divided in four subgroups: 1) patients with asymptomatic gallstones, 2) patients with uncomplicated symptomatic gallstones, 3) patients with primary complicated gallstone disease, and 4) patients with secondary complicated gallstone disease. Figure 1 provides an approximate representation of the incidence distribution across these groups, based on epidemiologic studies and the ratio of primary and secondary complicated gallstone disease found in chapter 4. (8-11)

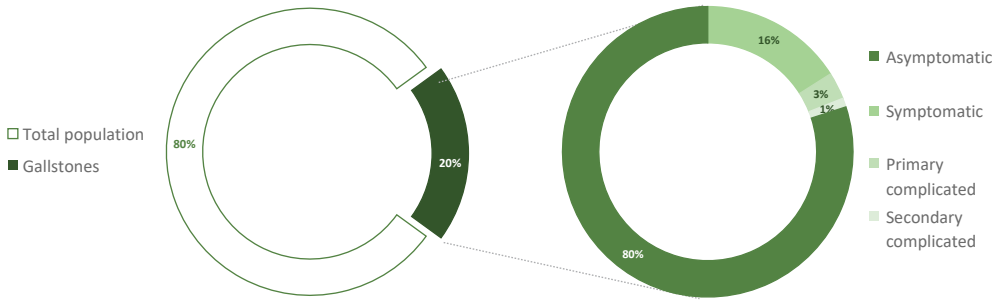

Figure 1.Total prevalence of gallstones (left) and distribution of gallstone presentations (right)

Our data indicate that the majority of complications present as primary complicated gallstone disease, underscoring the viability of conservative management at the outpatient clinic. Physicians should be cautious about offering cholecystectomy to patients with uncomplicated symptomatic gallstone disease, especially if complaints are vague. As with any intervention, potential benefits must be carefully weighed against the risks. Both our research and previous studies demonstrate that the outcomes regarding pain relief are uncertain, while the incidence of serious complications among outpatient clinic patients is low. (1, 5) The higher incidence of primary complicated gallstone disease highlights the importance of earlier risk identification. However, this remains challenging, as these patients are often not yet engaged with the healthcare system. The general practitioner may have an important role to play in this context.

General practitioners are the primary point of contact for patients, but most research on gallstone disease has been conducted in secondary care settings. This initial interaction shapes diagnostic trajectories and patient expectations, which may ultimately influence treatment decisions and outcomes in secondary care. (12, 13) Despite frequently managing patients with non-specific abdominal pain, general practitioners encounter gallstones relatively infrequently. A 2014 systematic review reported that 2.8% of con-

sultations at the general practitioner involve abdominal pain, and just 4% of these cases have a biliary or pancreatic origin. (14) Furthermore, prior studies suggest that no symptom reliably predicts the presence of gallstones in this setting. (15, 16) Our own findings in primary care, reported in Chapter 2 and 3, support this. Patients with a diagnosis of gallstone disease in general practice often present with multiple other abdominal complaints. We found that 57% of patients who received the diagnosis of gallstone disease in primary care also had a concurrent abdominal diagnosis. In a separate study, gallstones were confirmed via transabdominal ultrasound in only 37% of patients in whom general practitioners suspected gallstone disease. (17, 18) This raises important questions about over- or misdiagnosis and potential overtreatment in patients with abdominal complaints. These results highlight a critical gap in the diagnostic pathway: how to better distinguish patients who will truly benefit from referral or intervention. Future research should focus on refining diagnostic criteria and improving decision-making tools on the level of the general practitioner to reduce unnecessary imaging and streamline referrals. Greater clarity at the primary care level could not only improve outcomes but also optimize use of resources across the healthcare system.

Outcome assessment in gallstone disease

For effective treatment, there is a need for accurate assessment of complaints and the development of standardized scoring instruments. However, treatment outcomes are often evaluated using single-outcome measures. Traditional outcomes such as complication rates or readmissions overlook whether the patient's symptoms have improved. For instance, a technically flawless cholecystectomy may leave patients with unresolved abdominal complaints, revealing a gap between surgical performance and patient-reported outcomes.

To address this, we introduced the concept of a "textbook outcome" for patients with uncomplicated symptomatic gallstone disease. Gaining significance in recent years, textbook outcomes are composite measures that bundle multiple outcomes into a single, composite outcome. (19) These typically include clinical, technical, and increasingly patient-reported outcomes. Yet, until now, textbook outcomes had rarely been applied outside the context of malignant disease. In Chapters 6 and 7, we developed and applied a novel textbook outcome for patients with uncomplicated symptomatic gallstone disease. Using mixed methods, we defined the textbook outcome as 1) the absence of biliary colic, 2) no biliary complications, 3) no surgical complications, and 4) absence or reduction of abdominal pain. This proposes a shift toward outcome definitions that align more closely with patient reported outcomes. The primary factor preventing the achievement of textbook outcome was persistent pain, emphasizing the need for more refined selection criteria for cholecystectomy. The application of the novel meas-

ure in Chapter 7 shows its feasibility for benchmarking, and identified factors associated with achieving the ideal outcome. The strength of this textbook outcome, its inclusion of patient-reported outcomes such as persisting pain, also represents a key challenge for successful benchmarking. Currently, these data are not automatically collected. However, most hospitals nowadays use digital patient portals to communicate with patients. A practical approach to collecting data on persisting pain would be to engage patients through these portals and integrate the reported outcomes into the electronic health record. This could facilitate broader implementation and ensure that patient-reported outcomes are systematically included in performance benchmarking.

To date, evidence supporting the utility of textbook outcomes in enhancing clinical care for benign diseases is limited. Most existing validation studies are focused on surgeries for malignancies, retrospective in nature and thus susceptible to confounding due to selection bias. These studies show favourable outcomes in terms of survival after achieving textbook outcome, but patients achieving textbook outcomes often have fewer comorbidities, lower ASA scores, and more favourable disease stages. Additionally, survival advantages associated with textbook outcome achievement tend to emerge during first months of follow-up, suggesting confounding rather than a causal effect of better care. (20, 21) While textbook outcomes offer promise for benchmarking and quality improvement, their real value needs further investigation. Future studies should assess their predictive validity, responsiveness to quality interventions, and alignment with what matters most to patients.

To improve outcomes of patients with gallstone disease, we need to address functional disorders like irritable bowel syndrome and functional dyspepsia. These syndromes hamper outcomes of gallstone disease, as these patients more often have persistent pain. (2, 3) Existing questionnaires to evaluate these syndromes are extensive, impractical in daily use, and not validated to evaluate complaints caused by gallstones. To address this issue, in Chapter 8, we describe the development of a new questionnaire, the Gall-Q. A concise, 13-item questionnaire specifically designed to assess quality of life in patients with suspected gallstone disease. Importantly, the Gall-Q captures both biliary symptoms and functional gastrointestinal complaints (such as bloating and heartburn) enabling a more nuanced understanding of the patient's symptoms. The compact format makes it feasible for integration into daily clinical practice, facilitating more informed and individualized treatment decisions. At present, the utility of the Gall-Q is limited by its validation only in Dutch-speaking populations. To achieve wider applicability, future efforts should focus on cross-cultural validation and testing across diverse demographic and racial groups.

The roles of healthcare professionals and patients

Treatment decisions in healthcare result from a complex interplay between the physician, the patient, and broader societal influences, such as healthcare costs and environmental impact of healthcare. Within this interplay, the physician serves as the medical expert, with knowledge about the disease and available treatment options. The patient is the expert on his or her own values, preferences, and experiences. Societal factors, such as healthcare policy and resource allocation, further shape which treatments are accessible and considered appropriate. During clinical encounters, the physician is responsible for communicating relevant information about the condition and its possible management and incorporate the patient's expressed preferences. (22)

Navigating these various dimensions calls for a structured, collaborative approach to decision-making: shared decision-making. Ideally, treatment decisions are made together through such a process, which respects both medical expertise and patient autonomy. (23) Shared decision-making was first mentioned in the 1980s and gained traction in the 1990s, particularly in the trend towards more patient-centred care. Initially grounded in ethical principles, it reflects the fundamental right of individuals to decide what happens to their own body. (24) Over time, it emerged as a practical approach to improve care by involving patients in treatment decisions, especially when there is no clear 'best' treatment. (25)

With regard to broader societal influences, we are currently facing an environmental crisis that calls for more sustainable healthcare practices, alongside a growing elderly population that continues to cause annual increases in healthcare expenditures. (26, 27) Physicians carry a societal responsibility to help control healthcare costs and consider the environmental impact of their decisions. Every diagnostic test and surgical procedure contributes to both financial expenditures and environmental strain. (28, 29) Still, it is often difficult to resist intervention. Patients naturally seek the best possible treatment, and physicians strive to deliver it. Technological progress has led to substantial improvements in care, but also introduced higher costs. New interventions and medications are typically expensive at first and generate additional expenses through costs of implementation and necessary training of healthcare professionals. (30-32) Also, innovations can drive demand and lead to greater utilization of healthcare services. (33) As a result, total healthcare spending may rise, even when technological advancements reduce the cost of individual procedures. A similar pattern was observed in the early 1990s with the arrival of laparoscopic surgery. The introduction of laparoscopic cholecystectomy lowered the threshold for surgery, leading to a sharp rise in surgical volumes, but not to a significant decline in biliary complications. (34-38) This mismatch may be partly explained by an increased prevalence of gallstones due to risk factors such as obesity and hypercholesterolemia, but is more likely driven by patient demands

alongside expanding diagnostic and therapeutic possibilities leading to overtreatment. Additionally, a clear consensus for the treatment of patients with abdominal pain in the presence of gallstones is lacking. As pointed out by Wennberg et al., the absence of a clear consensus on optimal treatment strategies may lead to variation in clinical practice. (39, 40) When variation in clinical practice cannot be explained by patient characteristics or illness severity, it is considered unwarranted, because it leads to ineffective use of resources and higher costs. (41)

Shared decision-making and decision aids

Shared decision-making promotes informed, preference-sensitive decisions and may help reduce unwarranted practice variation. One practical tool to facilitate this process is the use of decision aids. These structured tools have been shown to improve disease-specific knowledge, reduce decisional conflict, and align treatment choices more closely with patient preferences. They may also encourage more conservative approaches and improve the appropriateness of surgical care. (42, 43) Chapter 10 shows that the majority of patients (86%) received their preferred treatment following the use of a decision aid. In our study, more severe symptoms were associated with a preference for surgical intervention. Notably, most patients expressed a preference for surgery, although conservative management may be an appropriate and viable option. Few studies have examined preference congruence. A 2014 review reported rates ranging from 49% to 70%, indicating that congruence in our study was relatively high. However, these rates varied widely across different diseases and clinical contexts, making direct comparisons challenging. (44) The tendency of patients to prefer surgical treatment may be influenced by several factors. For instance, as discussed before, patients' expectations are often shaped by the general practitioner, who may have already presented surgery as a definitive solution to their symptoms. Furthermore, patients frequently overestimate the benefits and underestimate the risks associated with medical tests and procedures. (45)

Chapter 9 presents the study protocol for a multicentre trial investigating the effect of decision aids in the context of elective surgeries for gallstones, inguinal hernias, knee osteoarthritis or hip osteoarthritis: The E-valuAID. The study addresses an important question: can decision aids reduce surgery rates without compromising outcomes? Several scenarios are plausible. First, if decision aids lead to reduced surgery rates without worsening patient-reported outcomes or increasing complication risks, this would argue strongly for broader implementation. Second, even if surgery rates remain unchanged, a demonstrated improvement in patients' confidence and satisfaction with their choices may justify the intervention, particularly if cost increases are marginal. Conversely and lastly, if decision aids increase surgery rates without improving outcomes, their value

would be more questionable unless accompanied by a clear gain in quality-of-life or reduction in adverse events. However, this scenario appears unlikely, given evidence from both Chapter 10 and previous research showing that decision aids tend to increase alignment between patient preferences and treatment decisions, while promoting more conservative approaches. (46)

Ultimately, decision aids and shared decision-making may serve not only as communication tools, but as potential mechanisms to reduce low-value care, promote patient-centred decisions, and minimize unwarranted practice variation. To fully realize their potential, decision aids may need to be tailored to the patient's individual clinical context and symptom profile. However, the impact of such personalized decision aids remains to be systematically evaluated. (47) Based on implementation of decision aids in the E-valuAID, several challenges have emerged. Logistically, patients often have to be identified prior to their first visit at the outpatient clinic, as introducing the decision aid during the first consultation can prolong the visit or necessitate a follow-up appointment. In addition, physicians can be reluctant due concern of lengthened consultation times and required changes in daily practice. These challenges are consistent with previously reported barriers to the use of shared decision-making. (48-50) Facilitating factors and barriers to the use of decision aids in the E-valuAID study will be further explored in a process evaluation involving physicians, patients, and outpatient clinic staff.

The before-mentioned chapters in this thesis contribute to our understanding of gallstone disease, outcome measurement, and the role of shared decision-making in elective surgery. At the same time, they raise new questions that warrant further research.

Future perspectives

- Developing evidence-based clinical guidance for primary care:

Currently, no specific guideline exists for managing abdominal pain in general practice, despite the wide range of potential aetiologies and diagnostic and treatment options. Developing such a guideline could support more appropriate diagnostic work-ups and enable more targeted referrals.

- Defining and validating primary complicated gallstone disease

Future efforts should focus on testing the hypothesis that a potentially important subgroup of patients presents with *primary complicated gallstone disease*. While some studies have suggested that complicated gallstone disease may be the initial presentation, robust evidence is lacking. (7) Such a study should include all patients with primary complicated gallstone disease (i.e., cholecystitis, choledocholithiasis, biliary pancreatitis, cholangitis), excluding those presenting with biliary colic or biliary malignancies. Medical histories should be reviewed for prior gallstone-related complaints and comple-

mented by questionnaires assessing earlier symptoms potentially attributable to gallstones. Subsequent studies may aim to identify patients at risk for primary complicated gallstone disease based on patient characteristics and radiological findings, enabling the development of predictive tools to detect those at risk. Additionally, a prospective cohort study could follow patients with incidentally found gallstones on either ultrasound or CT-scan to determine which individuals develop symptoms.

- Investigating the long-term consequences of cholecystectomy

Laparoscopic cholecystectomy is generally considered a relatively safe procedure, as mortality and severe short-term complications are rare. However, the long-term adverse effects of cholecystectomy remain poorly studied. Emerging evidence suggests possible associations with non-alcoholic fatty liver disease and an increased risk of colorectal cancer, particularly right-sided colon carcinoma, warranting further investigation. (51-54) For this objective, studies utilizing registry data, for example from the Netherlands Cancer Registry, could help identify associations with a history of cholecystectomy.

- Validating the gallstone textbook outcome and the Gall-Q across diverse populations

The novel textbook outcome for gallstone disease should be validated for its predictive accuracy, sensitivity to quality improvement measures, and alignment with patient-centred outcomes such as satisfaction and perceived benefit. The Gall-Q has so far only been validated in a Dutch population. For broader implementation, the questionnaire should also be validated in other languages and countries.

CONCLUSION

This thesis demonstrates that the current diagnostic and therapeutic trajectory for uncomplicated symptomatic gallstone disease is suboptimal across the entire clinical pathway. Many patients present with overlapping functional gastrointestinal symptoms, which contribute substantially to persistent complaints after surgery. Although laparoscopic cholecystectomy is considered a safe and effective intervention for complicated gallstone disease, its value in patients with uncomplicated disease remains ambiguous. The work strengthened outcome assessment through the development of a consensus-based Textbook Outcome and a validated, disease-specific questionnaire. Shared decision-making and the use of decision aids align care with patient preferences and may safely reduce surgical rates without compromising outcomes.

Collectively, these findings underline the need for more personalised patient care, clearer guidance in primary care, transparent communication about the uncertainty of postoperative outcomes, and structured outcome measurement. Implementing these insights in clinical practice can enhance symptom relief, minimise overtreatment, and improve the overall value of care for patients with gallstone disease.

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Appendices

Samenvatting

In dit proefschrift is galsteenlijden onderzocht over de gehele breedte van het zorgsysteem: van het zorggebruik in de eerstelijnszorg, via de opbrengst van een abdominale echo, de uitkomsten van de operatie in het ziekenhuis en de herziening van veelgebruikte uitkomstmaten, tot het gebruik van keuzehulpen ter ondersteuning van patiënten en artsen bij het maken van een behandelkeuze.

Deel I – Uitdagingen en onzekerheden in de diagnostiek en behandeling van galsteenlijden

Dit proefschrift bouwt voort op eerder onderzoek door onze onderzoeksgroep. In 2019 toonde de SECURE-trial dat een restrictief beleid voor cholecystectomie niet leidde tot slechtere uitkomsten dan gebruikelijke zorg, hoewel tot 40% van de patiënten na 12 maanden nog steeds buikpijn had. Net zoals de SECURE-trial, is merendeel van het onderzoek naar galsteenlijden uitgevoerd in de tweede lijn, in ziekenhuizen. In Nederland worden patiënten met een vermoeden van galsteenlijden echter meestal eerst gezien door de huisarts of op de eerste hulp. In dit proefschrift beschrijven wij twee studies naar patiënten met galsteenlijden in de eerstelijnszorg. In **Hoofdstuk 2** werden retrospectief 633 patiënten geïncludeerd die door hun huisarts de diagnose galsteenlijden hadden gekregen. Meer dan de helft van deze patiënten had in de drie jaar vóór of na de diagnose ook een andere abdominale diagnose geregistreerd gekregen. Aanvullend dossieronderzoek van 294 patiënten toonde dat ongeveer 80% van de patiënten werd verwezen naar het ziekenhuis en dat meer dan de helft van de verwezen patiënten nadien terugkeerde bij de huisarts met aanhoudende abdominale klachten, ongeacht of zij een galblaasverwijdering hadden ondergaan. Patiënten met eerdere abdominale diagnoses keerden vaker terug bij de huisarts.

Een echografie van het abdomen kan huisartsen ondersteunen bij de diagnose galsteenlijden door de aanwezigheid van galstenen te bevestigen. Eerder onderzoek liet echter zien dat geen enkel symptoom betrouwbaar de aanwezigheid van galstenen voorspelt. In **Hoofdstuk 3** beschrijven wij een prospectief cohortonderzoek waarin alle patiënten werden geïncludeerd die door hun huisarts werden verwezen voor een abdominale echografie vanwege een vermoeden van galsteenlijden. Van de 177 geïncludeerde patiënten bleek bijna twee derde geen galstenen te hebben. Om huisartsen te ondersteunen en overbehandeling te voorkomen, ontwikkelden we een predictiemodel voor de aanwezig-

heid van galstenen. De kans op galstenen nam toe bij hevigere pijn, koliekaanvallen, pijnfrequentie minder dan eenmaal per week en afwezigheid van zuurbranden.

Wanneer patiënten door de huisarts worden verwezen en in het ziekenhuis bij de chirurg komen kan een galblaasverwijdering (cholecystectomie) worden overwogen. Deze operatie wordt bij ongecompliceerd galsteenlijden uitgevoerd om patiënten van koliekaanvallen af te helpen, maar ook om complicaties van galstenen zoals acute cholecystitis, choledocholithiasis, biliaire pancreatitis of cholangitis te voorkomen. Om een weloverwogen beslissing voor een operatie te kunnen nemen, is het belangrijk om de gevolgen van niet opereren op de incidentie van biliaire complicaties te weten. In **Hoofdstuk 4** onderzochten de invloed van de COVID-19-pandemie op de incidentie van complicaties door galstenen en liesbreuken door de periode van maart-december 2020 te vergelijken met dezelfde periode in 2019. We vonden dat tijdens de pandemie minder patiënten in het ziekenhuis kwamen met galstenen of een liesbreuk. Daarnaast zagen we dat complicaties door galstenen toenamen, terwijl de incidentie van complicaties van liesbreuken onveranderd bleef.

Naast de mogelijke voordelen van een cholecystectomie, vervult de galblaas ook functies in het lichaam, die verloren gaan na verwijdering. Het verloren gaan van deze functie kan voor klachten zorgen, terwijl klachten die niet door galstenen werden veroorzaakt blijven bestaan. In **Hoofdstuk 5** onderzochten we daarom de prevalentie van klachten vóór en zes maanden na een galblaasverwijdering en keken wat voor klachten nieuw ontstonden of persisteerden na de operatie. De resultaten toonden aan dat koliekaanvallen bij 95% van de patiënten verdwenen, maar ruim een derde van de patiënten nog steeds buikpijn rapporteerde. Opvallend was dat vrijwel alle andere klachten, met uitzondering van frequente stoelgang en diarree, significant minder voorkwamen na de operatie. Ook klachten die initieel niet aan galstenen werden toegeschreven.

Deel II – Herziening van de evaluatie van uitkomsten en klachten bij galsteenlijden

Om de uitkomst van de behandeling van galsteenlijden te evalueren worden uiteenlopende maatstaven gebruikt. Veel vragenlijsten zijn aspecifiek en niet ontwikkeld voor deze patiëntenpopulatie, terwijl operatief succes vaak wordt beoordeeld aan de hand van chirurgische complicaties, heropnames of mortaliteit. Ook na een technisch succesvolle operatie kunnen klachten echter blijven bestaan. Om een completer beeld te krijgen, kan een combinatie van klinische en patiëntgerapporteerde uitkomsten daarom een betere inschatting van behandelresultaat laten zien.

Steeds vaker worden samengestelde uitkomsten gebruikt als kwaliteitsindicator, zogeheten *Textbook Outcomes*, waarin meerdere criteria moeten worden behaald om van een ideale uitkomst te spreken. Voor ongecompliceerd galsteenlijden ontbrak een

dergelijke maat. In **Hoofdstuk 6** beschrijven we een mixed-method studie waarin we deze ontwikkelden in 3 fases. Fase 1 bestond uit focusgroepen met experts om alle mogelijke uitkomsten te inventariseren. Op basis hiervan werden twee vragenlijsten opgesteld, één voor artsen en één voor patiënten. In fase 2 werden deze vragenlijsten verspreid; de vragenlijst voor artsen internationaal onder chirurgen en maag-, darm-, leverartsen, terwijl de andere vragenlijst werd verstuurd aan Nederlandse patiënten uit eerdere galsteenstudies. De uitkomsten van de vragenlijsten werden vervolgens gebruikt om met experts tot een definitieve Textbook Outcome te komen.

Deze werd als volgt gedefinieerd: het uitblijven van recidief biliaire kolieken met ziekenhuisopname, afwezigheid of vermindering van buikpijn, geen biliaire complicaties en geen chirurgische complicaties. Een post-hoc analyse liet zien dat de Textbook Outcome in ongeveer twee derde van de patiënten werd behaald, vaker na cholecystectomie (76% vs. 64%), met beperkte variatie tussen ziekenhuizen.

Na de hierboven beschreven ontwikkeling werd in **Hoofdstuk 7** onderzocht welke factoren geassocieerd waren met het behalen van de Textbook Outcome na cholecystectomie. De belangrijkste reden voor het niet behalen van de Textbook Outcome was persisterende buikpijn. Multivariabele analyse liet zien dat de aanwezigheid van typische biliaire koliek en de aanwezigheid van misselijkheid en/of braken tijdens de pijnaanval positief geassocieerd waren met het behalen van de gewenste uitkomst, terwijl een hogere pijnfrequentie (vaker dan eenmaal per maand) hier negatief mee geassocieerd was. Deze studie toont dat de nieuwe samengestelde uitkomst bruikbaar is als kwaliteitsmaat. Dit onderzoek zou daarnaast kunnen bijdragen aan een striktere selectie voor galblaasverwijdering.

Zoals hierboven reeds kort benoemd, werden symptomen van patiënten met galstenen vaak geëvalueerd met aspecifieke en uitgebreide vragenlijsten. Daarom bestond de behoefte aan het ontwikkelen van een ziekte-specifieke en praktische vragenlijst voor klinisch gebruik en onderzoek. **Hoofdstuk 8** beschrijft de ontwikkeling en validering van de Gall-Q; een praktische, ziekte-specifieke vragenlijst voor patiënten met ongecompliceerd galsteenlijden.

Dit onderzoek werd uitgevoerd in twee fasen. In de eerste fase werd de vragenlijst ontwikkeld door relevante items te selecteren uit bestaande gevalideerde vragenlijsten. Dit resulteerde in een instrument met drie domeinen: biliaire symptomen, niet-biliaire abdominale symptomen en dagelijks functioneren. In de tweede fase werd de vragenlijst gevalideerd in een cohort van 156 patiënten die een chirurgische polikliniek bezochten vanwege galsteenlijden. Twee items bleken onvoldoende te presteren op het gebied van interne consistentie en structurele validiteit, waarna een definitieve 13-itemversie overbleef. De Gall-Q toonde een goede interne consistentie (Cronbach's $\alpha = 0,79$), een duidelijke factorstructuur conform de beoogde domeinen en sterke convergente

en matige correlaties met respectievelijk de PAGI-SYM en HADS, wat de constructvaliditeit van het instrument ondersteunt. Het instrument kan bijdragen aan onderzoek en gedeelde besluitvorming, met name bij het onderscheiden van biliaire pijn en functionele gastro-intestinale klachten bij de beslissing voor cholecystectomie.

Deel III – Gedeelde besluitvorming

De onzekere uitkomsten van een cholecystectomie en het gebrek aan klachten die duidelijk aan galsteenlijden kunnen worden toegeschreven, maken afwachten een reële optie. Hierdoor is Shared Decision-Making voor het maken van een behandelkeuze in deze patiëntengroep uitermate geschikt. Hierbij bepalen arts en patiënt samen welke behandeling het meest passend is, op basis van medische informatie en persoonlijke voorkeuren van de patiënt.

Een veelbelovende manier om Shared Decision-Making te ondersteunen is het gebruik van keuzehulpen. Dit zijn gestructureerde, evidence-based instrumenten die patiënten informeren over verschillende behandelopties met hun voor- en nadelen, en hen helpen hun persoonlijke waarden en voorkeuren duidelijk te maken. In **Hoofdstuk 9** wordt het protocol beschreven van de *E-valuAID*, een multicenter onderzoek met een stepped-wedge design waarbij keuzehulpen worden geëvalueerd voor patiënten met een liesbreuk, galsteenlijden, knie- of heupslijtage. Het doel is te onderzoeken of het gebruik van keuzehulpen kan leiden tot beter geïnformeerde keuzes en daarmee een reductie van het aantal operaties. Daarnaast worden kosteneffectiviteit, patiëntgerapporteerde uitkomsten en bevorderende en belemmerende factoren voor het gebruik van keuzehulpen onderzocht. Op het moment van schrijven worden de analyses uitgevoerd, maar zijn er nog geen uitkomsten bekend.

Keuzehulpen werden in andere ziekenhuizen in Nederland reeds gebruikt en leken daar het operatiepercentage te kunnen reduceren. **Hoofdstuk 10** evalueert het gebruikt van keuzehulpen voor patiënten met galstenen of een liesbreuk in één ziekenhuis. Hierbij werd de overeenstemming tussen de voorkeur van de patiënt en de uiteindelijke behandeling onderzocht. Daarnaast zijn met multivariate regressieanalyse factoren geïdentificeerd die geassocieerd zijn met het ondergaan van een operatie. De overeenstemming tussen voorkeur en ontvangen behandeling was voor beide aandoeningen hoog, ongeveer 86%. Bij patiënten met galsteenlijden waren een voorkeur voor operatie en frequentere of hevigere klachten positief geassocieerd met het ondergaan van een operatie. Bij patiënten met een liesbreuk was bezorgdheid over chirurgische complicaties negatief geassocieerd met operatie, terwijl een voorkeur voor operatie positief geassocieerd was met het ondergaan van een operatie.

CONCLUSIE

Dit proefschrift laat zien dat er nog veel te winnen is in de diagnostiek en behandeling van ongecompliceerd galsteenlijden. Klachten van patiënten overlappen sterk met andere gastro-intestinale aandoeningen, wat in belangrijke mate bijdraagt aan persisterende klachten na een operatie. Hoewel laparoscopische cholecystectomie een veilige en effectieve behandeling is bij gecompliceerd galsteenlijden, blijft de meerwaarde bij ongecompliceerd galsteenlijden onduidelijk. Dit proefschrift draagt bij aan kennis over deze patiënten en de evaluatie van hun klachten, onder meer door de ontwikkeling van een Textbook Outcome en een nieuwe, specifieke vragenlijst. De bevindingen onderstrepen de noodzaak voor meer gepersonaliseerde zorg, duidelijke richtlijnen en gestructureerde uitkomstmetingen om overbehandeling te voorkomen en de zorg voor patiënten te verbeteren.

Data Management Plan

ETHICS AND PRIVACY

All chapters in this thesis were based on the results of research involving human participants, which were conducted in accordance with relevant national and international legislation and regulations, guidelines, codes of conduct and Radboudumc policy. All studies were conducted in accordance with the principles of the Declaration of Helsinki. (1)

The institutional ethical review committee CMO Radboudumc, Nijmegen, the Netherlands has given approval for the studies in **Chapter 2** (METC 2020-6871), **Chapter 3** (METC 2017-3306), **Chapter 4** (METC 2020-6739), **Chapter 8** (METC 2021-8262), and **Chapter 10** (METC 2017-3972). For these studies, a statement was obtained that the study was not subject to the Dutch Medical Research Involving Human Subjects Act (WMO), from the recognized Medical Ethics Review Committee 'METC Oost-Nederland'.

Data were used from previous two studies for **Chapter 5, 6 and 7**: 1) the SECURE-trial, and 2) the SUCCESS-trial. (2, 3) The SECURE-trial was subject to the Medical Research Involving Human Subjects Act (WMO) and was conducted in accordance with the ICH-Good Clinical Practice guidelines and was approved by the Medical Ethics committee AMC (METC 2013-129). For the SUCCESS trial the institutional ethical review committee CMO Radboudumc, Nijmegen, the Netherlands has given approval (METC 2017-3306) and a statement was obtained that the study was not subject to the Dutch Medical Research Involving Human Subjects Act (WMO).

Online informed consent was obtained at the start of the questionnaires from all participating patients or healthcare providers included within these chapters. Technical and organizational measures were followed to safeguard the availability, integrity, and confidentiality of the data.

Privacy measures

According to Dutch legislation, data collection from electronic patient files was performed by personnel with a treatment relationship with the patient or by the researchers upon consent by the study participant. The privacy of the participants in these studies was warranted by the use of pseudonymization and the pseudonymization key was stored on a secured network drive that was only accessible to members of the project

who needed access to it because of their role within the project. The pseudonymization key was stored separately from the research data.

DATA COLLECTION AND STORAGE

As noted, the studies in **Chapters 5, 6 and 7** were based on existing data that was previously published by our research group. (2, 3).

Data for **Chapters 2, 3, 4, 8, 9 and 10** were collected by local investigators and recorded in pseudonymized Case Report Forms (CRF). Data for **Chapters 8 and 9** were obtained by using Castor EDC (Amsterdam, The Netherlands) for secured online questionnaires. Data were exported from Castor EDC to SPSS (Chicago, USA).

Data from **Chapters 2, 3, 4, 5, 6, 7, 8, and 10** were stored and analyzed on the department server and in Castor EDC and are only accessible by project members working at the Radboudumc. For **Chapter 9**, data were stored and analyzed in the Azure DRE. These secure storage options safeguard the availability, integrity and confidentiality of the data. Paper (hardcopy) data is stored in cabinets on the department.

DATA SHARING ACCORDING TO THE FAIR PRINCIPLES

All studies were published and all chapters were published with open access. Radboudumc is the legal owner of the data. All data are stored in the Radboud data repository. The respective repositories are listed below:

Chapter 2: *Healthcare utilisation of patients with cholecystolithiasis in primary care: a multipractice comparative analysis*

DOI: 10.34973/yf46-5m70

Chapter 3: *Patients with Clinically Suspected Gallstone Disease: A More Selective Ultrasound May Improve Treatment Related Outcomes*
DOI: 10.34973/j4cz-8j79

Chapter 4: *The impact of surgical capacity shortages on disease-related morbidity in benign conditions: a comparative cohort study of gallstone and inguinal hernia care during the COVID-19 pandemic*
DOI: 10.34973/dtf0-x256

Chapter 5: *Persistent and new-onset symptoms after cholecystectomy in patients with uncomplicated symptomatic cholecystolithiasis: A post hoc analysis of 2 prospective clinical trials*
DOI: 10.34973/qys5-xz75

Chapter 6 and 7: *Textbook outcome in uncomplicated symptomatic gallstone disease*
DOI: 10.34973/44sv-7t59

Chapter 8: S*hort disease-specific quality of life questionnaire for patients with uncomplicated symptomatic cholecystolithiasis: Gall-Questionnaire*
DOI: 10.34973/16db-q297

Chapter 10: *The association between patients' preferred treatment after the use of a patient decision aid and their choice of eventual treatment*
DOI: 10.34973/j91n-mj57

Data will be kept for 10 years after publication of the study. The Gallbladder study group supports reuse of the data.

Title: Gallstones, No Stone Left Unturned

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Portfolio

Department: Surgery

PhD period: 01-11-2019 – 27-11-2026

PhD Supervisors:

dr. P.R. de Reuver

prof. dr. C.J.H.M. van Laarhoven

PhD Co-supervisor:

dr. F. Atsma

Training activities	Hours
Courses	
Radboudumc - eBROK course (for Radboudumc researchers working with human subjects) (2020)	26
Statistics for PhD candidates using SPSS (2020)	66
RIHS - Introduction course for PhD candidates (2020)	15
Scientific Writing for PhD Candidates (2020)	84
Radboudumc - Scientific integrity (2020)	20
IMM - The Art of Presenting Science (2020)	33
Design of Applied Medical Research (2021)	56
Conferences	
IHPBA World congress, New York (2022) including two poster presentations	66
Digestive disease days, Veldhoven (2021-3) including two poster presentations	24
Digestive disease days, Veldhoven (2021-8) including one oral and one poster presentation	24
Other	
Journal club Department of Surgery, once per month (2019-2021)	36
Research meeting Department of Surgery, weekly (2019-2021	50
Supervision of internships	
Supervision research internship (Master of Medicine) – Luuk Drager	28

Supervision research internship (Master of Medicine) – Britt Vermeulen	28
Supervision research internship (Master of Medicine) – Anna Groen	28
Supervision research internship (Master of Medicine) – Cléo Baars	28
Supervision research internship (Master of Medicine) – Rianne Arts	28
Supervision research internship (Master of Medicine) – Tamar van der Linden	28
Supervision research internship (Master of Medicine) – Marloes Berkers	28
Total hours	**696**

List of Publications

Thunnissen FM, Drager LD, Braak B, Drenth JPH, van Laarhoven CJHM, Schers HJ, de Reuver PR. Healthcare utilisation of patients with cholecystolithiasis in primary care: a multipractice comparative analysis. BMJ Open. 2021;11(11):e053188. doi:10.1136/bmjopen-2021-053188.

Thunnissen FM, Comes DJ, Geenen RWF, Riviere D, Latenstein CSS, Lantinga MA, et al. Patients with clinically suspected gallstone disease: a more selective ultrasound may improve treatment related outcomes. J Clin Med. 2023;12(12):4162. doi:10.3390/jcm12124162.

Thunnissen FM, Bluiminck S, van der Linden T, Berkers M, Polle B, Buyne O, et al. The impact of surgical capacity shortages on disease-related morbidity in benign conditions: a comparative cohort study of gallstone and inguinal hernia care during the COVID-19 pandemic. BMC Surg. 2026;26(1):203. doi:10.1186/s12893-026-03583-y.

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Thunnissen FM, Comes DJ, Latenstein CSS, Stommel MWJ, van Laarhoven CJHM, Drenth JPH, et al. A mixed-methods study to define Textbook Outcome for the treatment of patients with uncomplicated symptomatic gallstone disease with hospital variation analyses in Dutch trial data. HPB (Oxford). 2023;25(9):1000-1010. doi:10.1016/j.hpb.2023.05.005.

Comes DJ, **Thunnissen FM**, Latenstein CSS, Stommel MWJ, van Laarhoven CJHM, Drenth JPH, et al. Unraveling factors associated with textbook outcome after cholecystectomy in patients with uncomplicated cholecystolithiasis: a posthoc analysis of individual data of 1,124 patients. Surgery. 2024;176(2):414-419. doi:10.1016/j.surg.2024.04.026.

Thunnissen FM, Comes DJ, Kornmann VNN, de Nes LCF, van Workum FTWE, Wennmacker SZ, et al. Short disease-specific quality of life questionnaire for patients with uncomplicated symptomatic cholecystolithiasis: Gall-Questionnaire. BJS Open. 2025;9(2):zraf025. doi:10.1093/bjsopen/zraf025.

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Latenstein CSS, **Thunnissen FM**, Thomeer BJM, van Wely BJ, Meinders MJ, Elwyn G, et al. The association between patients' preferred treatment after the use of a patient decision aid and their choice of eventual treatment. Health Expect. 2020;23(3):651-658. doi:10.1111/hex.13045.

Furthermore

Thunnissen FM, Comes DJ, Latenstein CSS, Stommel MWJ, van Laarhoven CJHM, Drenth JPH, et al. Corrigendum to 'A mixed-methods study to define Textbook Outcome for the treatment of patients with uncomplicated symptomatic gallstone disease with hospital variation analyses in Dutch trial data' [Volume 25, Issue 9, September 2023, Pages 1000-1010]. HPB (Oxford). 2024;26(2):321. doi:10.1016/j.hpb.2023.11.006.

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Dankwoord

Het dankwoord houd ik graag bondig. Ik beperk mij tot de mensen die direct bij het onderzoek en de totstandkoming van deze thesis betrokken zijn geweest. Dat betekent uiteraard niet dat ik anderen die hier niet worden genoemd minder dankbaar ben.

Dr. **De Reuver**, Beste **Philip**, beste supervisor van het Radboudumc (in ieder geval van het jaar 2021). Onder jouw bezielende leiding komt aan ieder boek een eind, al duurt het bij sommigen wat langer dan bij anderen. Waar andere onderzoekers soms weken of maanden moeten wachten op feedback, duurt dat bij jou doorgaans eerder uren of dagen. Je betrokkenheid bij je onderzoekers gaat echter verder dan enkel op professioneel vlak, dat blijkt misschien wel het meest uit mijn laatste dag als onderzoeker. *Philip belt mij met een wat vreemd verzoek: "Ik sta nog te opereren, kun jij voor mij naar de garage waar mijn auto staat om die buiten het hek te zetten? Anders kan ik hem niet meer ophalen en ik heb hem echt nodig vanavond". Natuurlijk Phillip, geen probleem. Ik loop naar de garage, waar niemand iets wist van een auto van ene De Reuver. Ietwat verbouwereerd verlaat ik de garage. Aan het einde van de weg zie ik echter plots Philip staan, met de andere onderzoekers. Van een auto was geen sprake, Philip had voor mij een verrassingsafscheid georganiseerd.* Dank voor de begeleiding, het lachen en als laatste je geduld, ook toen onderzoek bij mij niet meer op de eerste plaats kwam.

Prof. dr. **Van Laarhoven**, beste **Kees**, dank voor je waardevolle inbreng tijdens onze besprekingen. Je hield ons scherp en liet ons regelmatig zaken vanuit een ander perspectief bekijken. Daarnaast was het leuk om onze ervaringen met de gezondheidszorg op de Antillen met elkaar te kunnen delen.

Dr. **Atsma**, beste **Femke**, ontzettend bedankt voor je steun en begeleiding. Je bent zeer grondig en hebt veel oog voor de details, waardoor je een waardevolle toevoeging was aan mijn promotieteam. Waar we er soms toe neigden om wat kort door de bocht te gaan, remde jij ons af waar dat nodig was. Je stond daarbij altijd open voor vragen. Tijdens onze meetings was er uiteraard aandacht voor de inhoud, maar had je ook altijd oog voor hoe het met mij ging, zeker tijdens de COVID-periode. Dat heb ik enorm gewaardeerd.

Beste **Wiebe**, **Wiebster**, manusje van alles. Ik ben onder de indruk van je nimmer aflatende ondernemingsdrang en van de producten die je bedenkt, ontwikkelt en maakt. Ook mijn onderzoek heb je visueel naar een hoger niveau getild, met je infographics en het ontwerp van dit boek. Dat je kundigheid op het gebied van ontwerp niet onopgemerkt

bleef, bleek wel toen je naar aanleiding van presentaties waarin ik jouw infographics gebruikte, door andere onderzoekers en een onderzoekersnetwerk werd gevraagd om afbeeldingen te maken en zelfs een website te ontwerpen. Dank voor al je creativiteit en enthousiasme!

Vivian, **Vief**, al vijf jaar samen en op naar nog veel langer! Nog steeds elke dag blij met je, ook al breng ik dat niet vaak (genoeg) onder woorden. Ik kan niet wachten op onze bruiloft volgend jaar en zie uit naar een leven verder met jou. Hoe dan ook, waar dan ook.

Lieve **papa** en **mama**, veel dank voor jullie onvoorwaardelijke steun en liefde.

Curriculum Vitae



Floris Martijn Thunnissen was born on 13 July 1994 in Utrecht, the Netherlands. He was born on the same day as his twin brother, Wouter. He grew up in Zeist, where he was raised by his parents, Peter and Marieke, and graduated from the Gymnasium in 2013. Although he had always aspired to study Medicine, the numerus fixus prevented him from starting immediately. He therefore first studied Physics at Utrecht University and Medical Sciences at Vrije Universiteit Amsterdam, before being admitted to study Medicine at the University of Amsterdam.

He started his Bachelor's degree in Medicine in 2016. The publication resulting from his Bachelor's thesis (Chapter 10 of this thesis) marked the beginning of his research career and provided the opportunity to start as a PhD candidate at the Department of Surgery at Radboud university medical center, under the supervision of Dr De Reuver. During his PhD, Floris was involved in several research projects and was responsible for the initiation and coordination of the E-valuAID trial.

After two years of full-time research, Floris returned to pursue his dream of becoming a physician and graduated in 2024. Shortly thereafter, he moved to Curaçao, where he worked for one year in the Department of Internal Medicine and its subspecialties. After returning to the Netherlands, he gained further clinical experience in Intensive Care and Gastroenterology at Rijnstate Hospital in Arnhem. These clinical experiences ultimately led him to pursue a career in Internal Medicine. He currently works in the Department of Internal Medicine at Jeroen Bosch Hospital in 's-Hertogenbosch.

In his spare time, he enjoys participating in and watching all kinds of sports, reading books, and cooking.



No Stone Left Unturned

F.M. Thunnissen

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