Comparison of Two Management Strategies, "Endoscopy First" and "Laparoscopic Cholecystectomy First", for Patients with Gallbladder Stones and Intermediate Risk for Choledocholithiasis: Study Protocol for a Diagnostic Randomized Trial

Ausra Aleknaite (ausra.aleknaite@santa.lt)
Vilnius Unversity, Faculty of Medicine https://orcid.org/0000-0002-2284-3629
Gintaras Simutis
Vilniaus universitetas Medicinos fakultetas
Juozas Stanaitis
Vilniaus universitetas Medicinos fakultetas
Tomas Jucaitis
Vilniaus Universitetas
Mantas Drungilas
Vilniaus Universiteto ligonines Santaros klinikos
Jonas Valantinas
Vilniaus universitetas Medicinos fakultetas
Kestutis Strupas
Vilniaus universitetas Medicinos fakultetas

Study protocol

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Abstract

Background: The optimal approach for patients with gallbladder stones and intermediate risk for choledocholithiasis still remains undetermined. Use of diagnostic endoscopic retrograde cholangiopancreatography should be minimized as it carries considerable risk of post-procedural complications. This study compares two different management strategies: intraoperative cholangiography and endoscopic ultrasound before laparoscopic cholecystectomy for patients with symptomatic cholecystolithiasis and intermediate risk for choledocholithiasis. Methods: It is a diagnostic randomized active-controlled single-centre clinical trial enrolling adult patients undergoing laparoscopic cholecystectomy due to symptomatic gallbladder stones with intermediate risk for choledocholithiasis. The risk for choledocholithiasis is calculated using an original prognostic score – Vilnius University Hospital Index. A total of 106 participants will be included and randomized into two groups. Evaluation of bile ducts using endoscopic ultrasound and endoscopic retrograde cholangiography on demand will be performed before laparoscopic cholecystectomy for one arm (“Endoscopy first”). Intraoperative cholangiography during laparoscopic cholecystectomy and postoperative endoscopic retrograde cholangiopancreatography on demand will be administered in another arm (“Cholecystectomy first”). Postoperative follow-up is 6 months. The primary endpoint is the length of hospital stay. Secondary endpoints will include accuracy of the different management strategies, adverse events of interventions, duct clearance and technical success of interventions (intraoperative cholangiography, endoscopic ultrasound, endoscopic retrograde cholangiography), costs of treatment. Discussion: This trial is planned determine which strategy is better approach for a patient with intermediate common bile duct stones risk and to define a simple to calculate and safe algorithm on managing choledocholithiasis. Trial registration: The trial is registered at ClinicalTrials.gov, identification number NCT03658863.

Background

A gallstone disease can be silent or symptomatic, as well as its most frequent complication – choledocholithiasis. About 10% to 18% of people undergoing cholecystectomy for gallstones have common bile duct (CBD) stones (1). Untreated choledocholithiasis can lead to acute biliary pancreatitis, acute ascending cholangitis, secondary sclerosing cholangitis, so it is essential to diagnose and treat it on time. Endoscopic retrograde cholangiopancreatography (ERCP) became a prominent diagnostic method for CBD stones since its introduction to clinical practice in 1970s (2). Later on, it was agreed that use of ERCP for diagnostic reasons should be minimized as it carries considerable risk (5 to 10%) of post-procedural complications (3). It is noticed that adverse events occur more often to patients with low risk of choledocholithiasis (4). A possibility to avoid using ERCP for diagnostic purposes came with introduction of new diagnostic less invasive procedures, such as magnetic resonance cholangiography (MRCP), endoscopic ultrasound (EUS), intraoperative cholangiography (IOC). Therefore, in the 2000s a discussion about more careful patient selection for ERCP procedure began as it should be left only for those with high probability of demand for therapeutical interventions, i.e. lithectomy, and patients with intermediate risk for choledocholithiasis should undergo additional investigation.

The most frequently used system to evaluate risk of choledocholithiasis is proposed in 2010 by American Society for Gastrointestinal Endoscopy (ASGE) (5). It already stratifies probability of CBD stones into low, intermediate and high risk categories, and suggests non-invasive investigations for intermediate risk group although its predictive values are not completely satisfying (6–10). These results encourage develop more accurate prognostic systems.

At the Centre of Abdominal Surgery of Vilnius University Hospital Santaros Klinikos an original prognostic index (Vilnius University Hospital index (VUHI)) is used for prediction of choledocholithiasis risk before laparoscopic cholecystectomy (LC). Recently we have evaluated its accuracy and determined new threshold values for low, intermediate and high risk groups (11). The intermediate risk group (risk for choledocholithiasis 25-75%) would benefit from additional examination before ERCP. Endoscopic ultrasound (EUS) and intraoperative cholangiography (IOC) are less invasive procedures with high accuracy identifying common bile duct stones. These procedures will be applied for patients with intermediate risk for CBD stones and will help to decide if ERCP is indicated.

We aim to compare LC with IOC to EUS as the first diagnostic biliary intervention in patients with intermediate risk of choledocholithiasis, to evaluate accuracy, technical success and safety of these two management strategies.

The hypothesis to assess is that LC with IOC (“Cholecystectomy first” strategy) will decrease both the length of hospital stay and morbidity by lessening the number of endoscopic investigations (EUS, ERCP) and herewith number of their possible complications, as well as decreasing the complications related to delayed cholecystectomy.

Methods/design

Design

This study is a single-centre randomized active-controlled trial comparing IOC and EUS on finding CBD stones for patients with intermediate risk of choledocholithiasis.

Ethical approval has been obtained from the Vilnius Regional Biomedical Research Ethics Committee, approval protocol number 158200-17-978-473.

Patients

Flowchart of the patients’ enrolment is displayed in Appendix, Figure 1.

Inclusion to the trial

Eligibility criteria are listed in Appendix, table 1. The trial will enrol 18-80 years old patients with cholecystolithiasis for whom laparoscopic cholecystectomy (LC) is indicated and who has intermediate risk for choledocholithiasis (VUHI 2.6 – 6.9 and one of predictors: dilated common bile duct, elevated

total bilirubin or suspected stone in CBD on ultrasound). We will not include pregnant, morbidly obese (body mass index >40) or severely ill (IV-VI class of American Society of Anesthesiologists physical status classification, contraindications for general anaesthesia or surgery) patients. Also, patients with anastomosis in upper gastrointestinal tract, known or suspected hepatitis of another origin (viral, toxic, etc.), other known cholestatic hepatopancreatobiliary disease will be excluded. We will rule out patients with known complications of gallstone disease, such as biliary pancreatitis, acute cholangitis, and II-III degree acute cholecystitis (as defined in Tokyo guidelines) (12,13).

Elimination from the trial

Patients will be omitted from the trial if a neoplastic condition will be found in the time of management, if a general status of a participant worsen and he needs urgent interventions not included in the trial protocol, if LC is converted into open cholecystectomy before IOC; if the patient refuses to participate in the trial.

Informed consent will be obtained from all study participants.

Setting

Participants will be enrolled and the trial will be carried out in Vilnius University Hospital Santaros Klinikos, a tertiary referral centre. The institution has experience in endoscopic ultrasonography, ERCP and intraoperative cholangiography procedures.

Randomization

Eligible patients who provide informed consent will be assigned to the groups “Endoscopy first” or “Cholecystectomy first” randomly, according to a pre-made sequence. The sequence is generated by a site *random.org* (Randomness and Integrity Services Ltd). The sequence was created using block randomisation of two elements, A and B (A - “Cholecystectomy first”, B - “Endoscopy first”) in a ratio 1:1. According to the sequence, sheets with group’s name are enclosed to opaque envelopes. Envelopes are numbered and the number of the envelope is patient’s number in the trial. When a new participant of the trial is enrolled the topmost envelope is opened by one of investigators and the participant is randomised into the specified group.

Procedure

The participants of the trial will undergo CBD evaluation depending on the group assignment. For the group “Endoscopy first” EUS is used to evaluate bile ducts. If stones in extrahepatic bile ducts are seen ERCP and lithectomy is performed during the same anaesthesia. LC is performed after endoscopic procedures as soon as possible. In the group “Cholecystectomy first” LC with IOC is performed. If stones are found postoperative ERCP with lithectomy is applied (during cholecystectomy if common bile duct is completely blocked or as soon as possible).

EUS is performed with linear or radial Olympus ultrasound endoscopes. CBD, pancreatic head and adjacent structures are visualised from duodenal bulb and descending duodenum. EUS is considered positive for CBD stone(s) when a constant hyperechogenic lesion with acoustic shadowing is seen in CBD projection.

ERCP procedures are performed by experienced endoscopists (each has more than 5 years of experience in ERCP and more than 500 procedures done). Olympus side-viewing endoscopes TJF-160VR are used. Primary deep selective cannulation of CBD is performed with sphincterotome or cannula and guidewire technique. Diatrizoate (Urografin) and iohexol (Omnipaque) are used as a contrast media. Endoscopic sphincterotomy is performed over a guidewire technique with Olympus pull-type sphincterotome. Papillary balloon dilation using a through-the-scope balloon catheter is applied when stricture is indicated. Stones are removed using a retrieval balloon catheter and/or a Dormia basket. Complete clearance of CBD is documented with a balloon catheter cholangiogram at the end of the procedure. ERCP is considered positive when a filling defect(s) is seen in cholangiogram and/or a stone(s) evacuates from CBD. ERCP is considered unsuccessful when cannulation of bile ducts is technically impossible.

All patients will undergo a standard four-port LC: a 10-mm port at the umbilicus, a 10-mm port at the subxyphoid, a 5-mm port at the bottom of the gallbladder, and a 5-mm port at the right epigastrium. A 30-degree laparoscope is used for intra-abdominal visualization. After exposure and identification of the elements of the hepatocystic triangle, a small transverse cut is performed in the cystic duct close to the gallbladder infundibulum with laparoscopic scissors. A 4-French cholangiogram catheter is placed in 5 mm Cholangiography Fixation Clamp and then inserted into the cystic duct. After verifying the absence of leakage at the catheter insertion site, contrast media (Urografin) diluted in NaCl 0.9% with a 1:1 ratio in a 20 ml syringe is injected under fluoroscopic vision (C-arm, Siemens GmbH, Germany). Cholangiograms are assessed by the operating surgeon and radiologist. IOC is considered positive when there is a filling defect(s) or lack of contrast evacuation to duodenum.

All the procedures of the trial are outlined in Appendix, table 2 (SPIRIT Figure).

Blinding

As both management strategies – endoscopic evaluation and intraoperative examination – differ in nature and post-procedure effect on a patient, complete blinding of participants is not possible. Before enrolment to the trial the participant, treating clinician and investigator will not know to which group participant is assigned.

Follow-up

The participants are followed while treated inpatient after LC (short term surveillance) and for 6 months after the hospitalisation (long term surveillance). In the short term surveillance period post-procedural adverse events, signs of cholestasis, need for repeated procedures are recorded. In the long term

surveillance period participants are encouraged to contact investigators if any symptoms of recurrent cholelithiasis are suspected. 6 to 12 months later participants will be contacted via phone or email. Their health status will be evaluated using Medical Outcomes Study Short Form Health Survey (SF-36) (14) with additional questionnaire on possible symptoms of choledocholithiasis (presented in Appendix, Questionnaire 1). If any symptoms of possible gallstone disease are observed the participant is invited for additional investigation (biochemical blood tests, transabdominal ultrasound, MRCP on demand).

Outcomes

The primary endpoint is the length of hospital stay - duration from enrolment into the trial to discharge, in days.

Secondary endpoints will include:

1) Diagnostic accuracy of the different management strategies (proportion of correctly diagnosed (true positive and true negative) cases in all sample, time frame – 6 to 12 months);

2) Technical success of diagnostic and therapeutic biliary procedures (IOC, EUS, ERCP) (during active treatment period)

a) For IOC: successful cannulation and contrast media injection into CBD;

b) For EUS: successful visualisation of CBD;

c) For ERCP: successful cannulation and contrast media injection into CBD;

d) Successful CBD clearance.

3) Postoperative course and possible complications of treatment (time frame – up to one month):

a) Adverse events of endoscopic interventions and IOC:

i) Bleeding - hematemesis and/or melena or hemoglobin drop >20 g/l;

ii) perforation - evidence of air or luminal contents outside the gastrointestinalf tract;

iii) post-ERCP pancreatitis - new or worsening abdominal pain persisting for at least 24 h and requiring analgesics after ERCP in conjunction with an elevation in serum amylase or lipase levels greater than three times the normal upper limit (15), (16);

b) assessment of postoperative course by Clavien - Dindo classification of surgical complications (17).

4) Costs of treatment (charges of diagnostic procedures, invasive procedures, surgery, antibacterial treatment if needed and hospital charges).

Statistical considerations

Sample size was calculated in reference to collected data on management of choledocholithiasis in the trial centre, Vilnius University Hospital Santaros Klinikos (11). In our previous study mean treatment duration for different management strategy groups (LC-IOC first and ERCP-first) were 5.37 and 7.13 days, with standard deviations 2.5 and 2.8 respectively, these findings were used to calculate requested sample size. A program G*Power version 3.1.9.2 was used for calculations. It was calculated as for two-tailed t test for means of two independent groups. Significance level was selected to be 0.05, power 0.8. Required sample size is 74: two groups with 37 valid participants each.

The endpoints in different management groups will be analysed using chi-square test or t test for independent means. Two-sided hypotheses are to be checked and a p-value <0.05 will be considered statistically significant. If the distribution is non-normal, a transformation such as the logarithm or square root function can be applied to get a normal distribution or nonparametric tests, e. g. Mann – Whitney test can be used. To evaluate achieved power a post hoc power analysis calculation will be performed. As for the primary outcome a difference of two days of hospital stay would be considered as clinically meaningful.

Discussion

In the era of minimally invasive surgery and personalized medical care the optimal cost-effective strategy for the management of patients with symptomatic gallstones and suspected choledocholithiasis is not categorically defined yet.

The whole approach to patient with gallbladder stones consists of a few steps: evaluation of probability of stones in CBD, visualisation and evacuation of the stones when present and treatment of cholecystolithiasis itself (18). There are a few main clinical dilemmas in the management of choledocholithiasis: which patients should be investigated for CBD stones and what is the optimal way to treat it – single-stage (LC with intraoperative CBD evaluation) or two-stage (preoperative ERCP followed by LC) technique.

First, it is essential to define the criteria for different risk groups. Whilst the majority of recent trials evaluating accuracy of choledocholithiasis prediction refer to ASGE guidelines we performed an analysis of seven different studies on this prognostic system and predictive values of high risk criteria were quite mediocre: general sensitivity was found to be 52.4%, specificity 60.8%, positive predictive value 65.6%, negative predictive value 47.4%, accuracy 55.9% (11). At the centre of this trial an original prognostic index (VUHI) is used for prediction of choledocholithiasis risk before LC since 1999. It is calculated by formula VUHI = A/30 + 0.4×B, where A - total bilirubin concentration (mcmol/l), B - CBD diameter measured by ultrasound exam. Results of our previous study showed that VUHI had comparable and, at some parameters, superior performance than the prognostic system of ASGE guidelines (11). The most modest measure was the specificity of VUHI (54%, whilst sensitivity was 80.5%). This implied that earlier threshold of the index was kind of weak spot in this evaluation system. Newly generated model for predicted probability of choledocholithiasis sets limits for intermediate risk group, i.e. determines which

patients should undergo additional non-interventional investigation. We chose thresholds for intermediate risk group to be at 25 and 75% of probability for CBD stones considering that upper limit of 50% as in ASGE guidelines would still leave certain amount of patients who will receive unnecessary ERCPs. Latest EASL (The European Association for the Study of the Liver) guidelines also state that patients with intermediate probability should undergo further evaluation with EUS or MRCP but do not define what this intermediate probability is (19). Meta-analyses showed that these two diagnostic procedures are quite comparable but EUS has better diagnostic accuracy (20,21). Just one trial comparing EUS and IOC was found in PubMed database and showed better predictive values of IOC (22). Considering that this study was performed twenty years ago and imaging technologies have advanced since then it is worth to compare these two methods once again. When comparing IOC with ERCP as a diagnostic procedure, systematic review of ten trials by Gurusamy et al. showed slightly higher sensitivity of IOC with no difference in specificity (23).

The next step is to choose optimal management strategy. In the aforementioned study we assessed effectiveness of different approaches (LC with IOC and ERCP “on demand” versus preoperative ERCP with sphincterotomy and necessary therapeutic interventions followed by LC). Some advantages in both strategies were found: there were less missed stones and false positive cholangiographies in ERCP-first group, meanwhile LC-IOC group had less ERCP related complications and mean length of hospital stay in this group was shorter, in most cases reflecting no need to wait for another procedure (11). Barreras González JE et al. also find these two strategies comparable in efficacy (24). Moreover, meta-analyses of various different trials show that there is no significant difference in the mortality, morbidity, retained stones, and failure rates between the single-stage and two-stage choledocholithiasis management (1,25). The main drawback of preoperative ERCP plus LC strategy against various single-session approaches (intraoperative ERCP, LC with laparoscopic bile duct clearance, open bile duct clearance) is the time: usually there is waiting period between two procedures which prolongs duration of hospital stay and slightly increases the risk to develop recurrent biliary events and cholecystitis (19,26,27). The reduced length of hospital stay was the only significant advantage of intraoperative ERCP found by Cochrane systematic review when comparing single stage and two stages approach in another way – laparoscopic – endoscopic *rendezvous* versus preoperative endoscopic sphincterotomy (28). A recent meta-analysis by Ricci et al. of four laparoscopic and endoscopic techniques for managing gallstone disease with biliary duct calculi showed that safest and the most successful approach is combined LC with intraoperative ERCP (29). However, one of the biggest limitations to single-session ERCP and LC is difficult coordination of medical personnel, equipment and location of procedure (30,31). Despite these restraints a large survey of general surgeons in USA showed that the majority of respondents preferred ERCP to laparoscopic CBD exploration for the management of choledocholithiasis (32).

This trial is aimed to answer the question which one of the two strategies – preoperative EUS or LC with IOC is the optimal solution for intermediate risk of CBD stones. We intend to compare various aspects of two ways of choledocholithiasis management: from accuracy to cost and time efficiency. Thresholds of different risk groups also will be verified prospectively. We tend to presume that LC with IOC could be the preferred management strategy because of the saved time comparing with two-stage strategy so the

study is planned as a superiority trial. We chose to designate two days' duration of hospital stay as a minimal important difference between the two groups because it causes a significant increase of management costs and is barely influenced by non-medical reasons which can happen when difference is chosen to be one day. If the difference of inpatient treatment duration is not statistically significant there are yet other outcomes to be evaluated to compare these two strategies. Overall, this trial is planned to define a simple to calculate and safe algorithm on managing choledocholithiasis.

Trial status

Trial protocol TLA02, version 2.

Trial started on December 15, 2017, anticipated trial completion December 15, 2020.

Trial is registered at ClinicalTrials.gov, identification number NCT03658863.

List Of Abbreviations

ASGE – American Society for Gastrointestinal Endoscopy
CBD - common bile duct
ERCP – endoscopic retrograde cholangiopancreatography
EUS – endoscopic ultrasound
IOC – intraoperative cholangiography
LC – laparoscopic cholecystectomy
MRCP – magnetic resonance cholangiopancreatography
VUHI – Vilnius University Hospital index

Declarations

Ethics approval and consent to participate

Ethical approval has been obtained from the Vilnius Regional Biomedical Research Ethics Committee, approval protocol number 158200-17-978-473.

Informed consent will be obtained from all study participants.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This trial was conducted with no external funding and is performed on the resources of the hospital as the trial is a part of PhD research of one of investigators (AA) and the centre of the trial is a university hospital. The approval to carry out the trial on resources of the hospital was obtained and signed as a contract between the hospital and investigators.

Authors' contributions

GS and AA conceived the project, designed the study, drafted the manuscript, and approved the final submission. GS, AA, JS, TJ and MD arranged inclusion criteria, participates in patients' selection and enrolment. AA performed sample size calculation. KS and JV helped design the study, revised the manuscript, and approved the final submission. All authors read and approved the manuscript.

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Appendix

Table 1. Eligibility criteria

Inclusion Criteria	
	Age 18-80 years
	Symptomatic cholecystolithiasis
	Intermediate risk for choledocholithiasis (VUHI 2,6 - 6,9 and one of predictors: dilated common bile duct >6mm, elevated total bilirubin >21 mcmol/l or suspected stone in CBD on ultrasound).
Exclusion Criteria	
	acute cholangitis, as defined in Tokyo guidelines 2013 (12)*;*
	moderately severe or severe biliary pancreatitis as defined in revised Atlanta classification (33)
	acute cholecystitis, degree II-III by Tokyo guidelines 2013 (13)*;*
	anastomosis in upper gastrointestinal tract;
	known cholestatic hepatopancreatobiliary disease;
	known or suspected hepatitis (viral, toxic, etc.);
	contraindications for general anaesthesia or surgery;
	IV-VI class of ASA physical status classification;
	morbid obesity (body mass index > 40);
	pregnancy;
	patient's refusal to participate in the study.

Table 2. Enrolment, interventions and surveillance procedures

	Study period				
	Enrolment	Allocation	Post-allocation		
			Management	Short term surveillance (inpatient)	Long term surveillance (6 months)
Recruitment:					
Eligibility screen	x				
Informed consent	x				
Randomisation		x			
Management strategy:					
"Endoscopy first"			x		
"Cholecystectomy first"			x		
Assessments:					
Bilirubin concentration	x			on demand	on demand
Ultrasound	x			on demand	on demand
Surgical records			x	x	
Postoperative records			x	x	
Interview with patient					x

Questionnaire 1. Symptoms of possible choledocholithiasis

You had a gallbladder removal operation performed in Santaros Klinikos 6 months ago. You have consented to participate in the clinical study on risk of bile duct stones. Please answer to following questions on your health status after the operation.

1. Have you had any pain in the upper right part of your abdomen or in other areas? If yes, please specify.
2. Have you become jaundiced (have you noticed that your skin or eyes turned yellow)?
3. Have you had fever without any clear reason (e.g., common cold)?
4. Have you had doctor appointment for any of those reasons?
5. If yes, what investigations were performed and what diagnosis was stated?

6. If you had any of those symptoms, would you agree to arrive at Santaros Klinikos for additional investigation – abdominal ultrasound and blood tests?

Figures

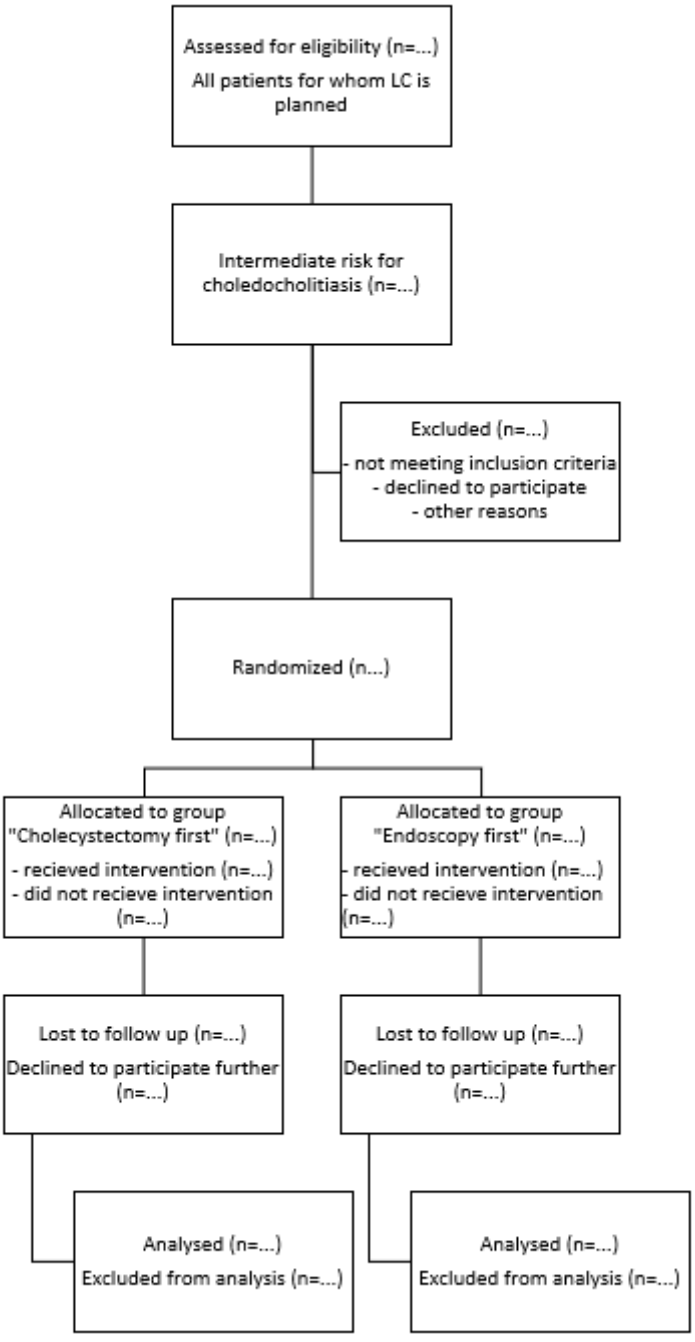

Figure 1

Flowchart of the study.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SPIRITChecklist.doc