Which pre-operative findings translate to a positive intra-operative cholangiogram?

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Declaration

I, **Mohamed Ali M Elmusbahi**, hereby declare that the work on which this thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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Dr Mohamed Ali M Elmusbahi

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Part A - Study protocol

Study title: Predictive model correlating pre-operative findings with intra-operative cholangiogram results

Principle Investigators: Dr JC Kloppers, Dr JH Klopper

Co-investigator: Dr Mohamed Ali M Elmusbahi

Introduction and background: The first intra-operative cholangiogram series was published in 1931 by Mirizzi during the exploration of the common bile duct (CBD) for stones. This development came at a critical period when complications following biliary surgery were both common and serious[1].

An intraoperative cholangiogram (IOC) is the fluoroscopy image of the biliary tree during laparoscopic cholecystectomy, which can be done routinely or selectively[2].

There is no convincing data to suggest that routinely performed IOC reduces the incidence of retained CBD stones after laparoscopic cholecystectomy. It, however, increases cost and prolongs operative time[3]. Furthermore, imaging misinterpretation can lead to false-positive studies and unnecessary post-operative invasive procedures.

The indication for selective IOC would be abnormal liver enzymes and/or dilated biliary tree on pre-operative ultrasound[4]. This group of patients would be categorised as intermediate risk for CBD stones. Patients with mild acute biliary pancreatitis would also fall into this group. Jaundice patients would be high risk and thus justify pre-operative endoscopic retrograde cholangiopancreaticogram (ERCP)[5]. This reflects our current practice[6].

A filling defect on IOC can lead to operative CBD exploration, post-operative ERCP or observation with clinical and imaging follow up[7,8]**.**

As seen in the literature, there are no universal guidelines for the use of IOC. There are two other role-players in MRCP and endoscopic ultrasound for the pre-operative imaging of the bile duct[9], but in a resource scares environment, this cannot be accessed routinely. Our study will investigate if the patients currently selected for IOC (deranged liver enzymes, dilated

biliary tree & mild acute pancreatitis) have their management changed by this procedure. Primary endpoint being further positive intervention done in the case of a positive finding on IOC (filling defect or contrast not draining).

Research question: Which pre-operative finding correlates with a positive IOC leading to further interventions?

Study Objectives:

Primary Objective: Which pre-operative finding correlates with a positive IOC leading to further interventions?

Secondary objectives: Follow up negative IOC's for any adverse outcomes.

Materials and methods

Study design: A retrospective cohort analysis of a prospectively maintained database.

Study settings: Operative databases of both the Acute Care Surgery Unit and Hepatobiliary Surgery Unit will be used to identify all patients who underwent IOC during laparoscopic cholecystectomy (lap chole). Data on patients' demographic characteristics, indication for lap chole, history of pancreatitis, history of jaundice with pre-operative findings of LFT's and ultrasound will be collected. IOC findings will be documented and postoperative course of these patients. The information on the database will be exported into an Excel spreadsheet for analysis.

Time Period: From 1st January 2015 to 31st December 2016

Data Analysis: Data will be described in means and standard deviations for normally distributed data and medians and confidence intervals for non-parametric data.

Justification for the chosen timeline: Two-year period where electronic patient records are available**.** The start date was when the database was implemented, numbers needed to fulfil sample size calculations, or previously reported studies had used this timeframe.

Inclusion Criteria: All patients who were investigated with an IOC during laparoscopic or open cholecystectomy.

Exclusion Criteria: Incomplete reporting of IOC or bile duct injuries.

Ethics approval: Approval will be obtained from the UCT Human Research Ethics Committee and the Departmental Regulatory Board (DRB). Data and all appropriate documentation will be stored for a minimum of five years after the completion of the study, including the follow-up period.

Consent: No consent is required since this a retrospective analysis of patient records

Confidentiality: The Principal Investigator will preserve the confidentiality of participants taking part in the study in compliance with data protection legislation.

Anonymity will be ensured with the use of a master code, which will be kept in a separate secure filing cabinet. All computers will be password protected.

Indemnity: UCT holds a non-negligent harm insurance policy that applies to this study.

Sponsor: UCT will act as the main Sponsor for this study. Delegated responsibilities assigned to the research team running this study will be documented.

Funding: None

Audits: The study may be subject to inspection and review by UCT CRC under their remit as Sponsor and other regulatory bodies to ensure adherence to South African Good Clinical Practice if required.

Publication Policy: Authorship will be based on substantial contribution to the conception, design, analysis, interpretation of data, drafting, and approval of the version to be published.

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Part B - Literature review

Choledocholithiasis

Literature search strategy

A structured literature review was completed searching the electronic databases of PubMed, Google Scholar, and *UpToDate* using the search thread (cholelithiasis) or (choledocholithiasis) or (intraoperative cholangiogram). Additional manual searches of the Cochrane Library were performed. References were crossed checked. Only human studies in English were included.

Incidence and clinical manifestations

The first laparoscopic cholecystectomy was performed in 1990. Since then laparoscopic cholecystectomy has become one of the most common surgical operations worldwide[1]. Cholelithiasis affects up to 21% of the general population and more than 75% are females[2]. Choledocholithiasis is found in 11 to 20% of patients with cholelithiasis, a significant proportion may be asymtomatic[3]. The majority of cases of choledocholithiasis result from the migration of gallbladder stones (secondary choledocholithiasis) to the common bile duct and less commonly from stone that forms in the bile duct (primary choledocholithiasis).

Pain and obstructive jaundice are the most common features. The pain differs from biliary colic in that it lasts longer with sudden relief when the common bile duct (CBD) stone pass or being removed. Obstructive jaundice associated with or without pain is also a common presentation. Asymptomatic stones are not an uncommon presentation which can be detected with ultrasound (U/S) or abnormal liver function test (LFT)[4]. According to the presenting symptoms, it is classified as an uncomplicated - or complicated presentation. Some patients have a phenomenon called the "ball-valve" effect; it is an intermittent pain as a result of a small stone which causes a transient blockage or floating in CBD[5].

The most serious complications are the result of bile flow obstruction which lead to infection of bile causing ascending cholangitis. Gallstone pancreatitis is a result of pancreatic duct obstruction by a CBD stone, which leads to backflow of bile to the pancreatic duct and acinar cell damage[6].

Diagnosis

In spite of a wide variety of examinations and investigations there are two necessary questions in the intermediate group to consider:

1) How to cost-effectively diagnose a CBD stone
2) The best strategy for dealing with a CBD stone once it is detected

The diagnosis of CBD stones are made by history, clinical examination, laboratory tests (LFT, and serum lipase) and imaging (transabdominal U/S, MRCP, ERCP, EUS, and IOC)[7].

Liver enzymes ALT and AST might be raised early in the passage of CBD stones. Progressively, liver function tests are typically elevated in a cholestatic picture, with increases in bilirubin and ductal enzymes ALP and GGT more prominent than elevation in serum ALT and AST.

Numerous authors have tried to evaluate the predictive value of liver function tests for choledocholithiasis[8–10]. A meta-analysis of 22 studies estimated the predictive role of multiple examination findings and criteria used in the identifications of choledocholithiasis, including bilirubin and ALP[12]. An increase in bilirubin level had a sensitivity of 69% and a specificity of 88% for diagnosing CBD stones. For elevations in serum ALP, the values were 57% and 86%, respectively.

A study of 1002 patients, who underwent laparoscopic cholecystectomy for cholelithiasis, evaluated five liver function tests for predicting choledocholithiasis: GGT, ALP, total bilirubin, ALT, and AST[10]. The sensitivities ranged from 64% for AST to 84% for GGT, and the specificities ranged from 68% for ALT to 88% for bilirubin. Raised GGT, ALP, and bilirubin levels were independent predictors of a CBD stone on multivariable analysis.

Since liver function tests may be elevated due to a wide variety of causes, the positive predictive value of raised liver function tests is inadequate. Oppositely, the negative predictive value of normal liver function tests is high. Accordingly, normal liver function tests play a more significant role in excluding choledocholithiasis than elevated liver tests play in diagnosing of choledocholithiasis.

Images

Several imaging modalities can confirm the presence of CBD stones

- Transabdominal ultrasound (U/S)
- MRCP
- ERCP
- EUS
- IOC

Transabdominal U/S is the initial imaging test of choice for upper quadrant pain, which can evaluate cholelithiasis or choledocholithiasis and dilatation of the CBD. It is cheap, non-invasive and can be performed by the bedside[11]. The sensitivity ranges from 20% to 90% for detecting choledocholithiasis as it is operator depended with a specificity of 91%[12]. Ultrasound has a very low sensitivity for distal CBD stones which usually are obscured by bowel gas in the image field[13]. A dilated CBD is suspicious for a distal CBD stone, but it is not specific for choledocholithiasis[14]. A normal CBD on U/S is about 6 mm[15,16], the probability of CBD stones increased with an increase of CBD dilatation:

0 to 4 mm: 3.9%

4 to 6 mm: 9.4%

6 to 8 mm: 28%

8 to 10 mm: 32%

>10 mm: 50%

CBD diameter increases with age, so a patient above 60 years could have a normal CBD above 6 mm[17–19].

Figure 1 Abdominal ultrasound showing a dilated common bile duct (11 mm)[20].

Figure 2 Stone (arrow) and dilated CBD[21].

Endoscopic retrograde cholangiogram (ERCP) is an invasive test which carries complications such as bleeding, perforation and acute pancreatitis. Therefore, expertise is required to perform the procedure. Previously it was used for diagnosis and therapy for CBD stones, but now it is reserved for the high-risk group. ERCP has a sensitivity for CBD stones of 80–93% and specificity of 99–100%[22,23].

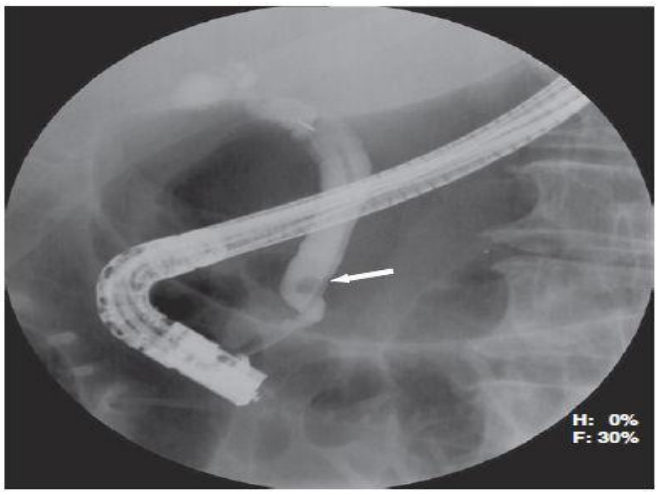

Figure 3 ERCP demonstrate a stone (arrow) within CBD[24].

Magnetic resonance cholangiopancreatography (MRCP) is a non-invasive modality and does not require an injection of a contrast medium into the biliary system which makes it very safe. The disadvantage of MRCP is its diagnostic nature and it does not permit interventions like stone extraction. It also has a lower resolution than ERCP and therefore small stone (<4 mm) can be missed[25]. MRCP has sensitivity 92% and specificity 94%[26].

Figure 4 MRCP shows a stone within the distal CBD (arrow)[27].

Endoscopic ultrasound (EUS) is less invasive than ERCP and has a sensitivity of 94% and specificity of 95% in a validated user[28]. Due to its unavailability, it is hardly ever used in the diagnostic workup for CBD stones.

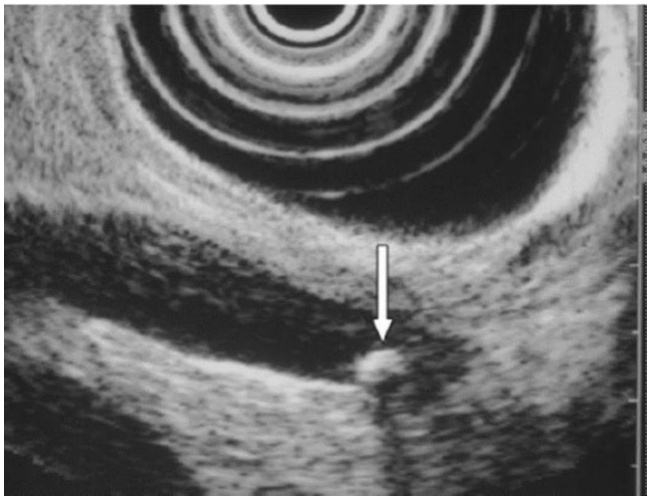

Figure 5 EUS is demonstrating stone (arrow) within CBD[29].

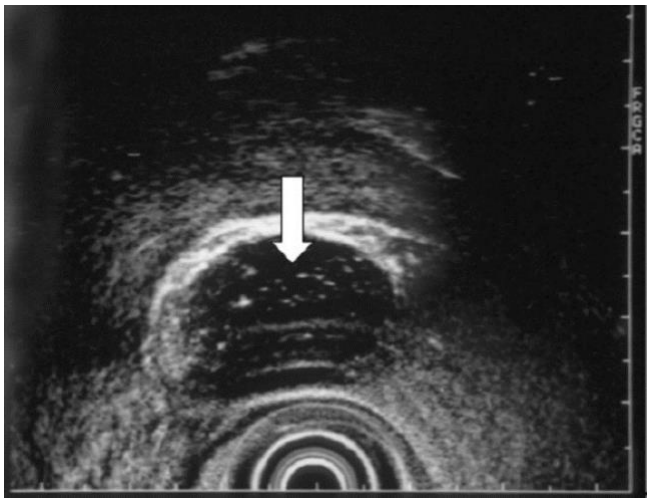

Figure 6 EUS shows microlithiasis (arrow) within GB[29].

Intra-operative ultrasound (IOU) is another approach for detecting CBD stones with a sensitivity of 90% with the advantage of no CBD entry. It implies less bile duct injuries compared to IOC but requires surgeon's expertise and comfort with the techniques[30,31].

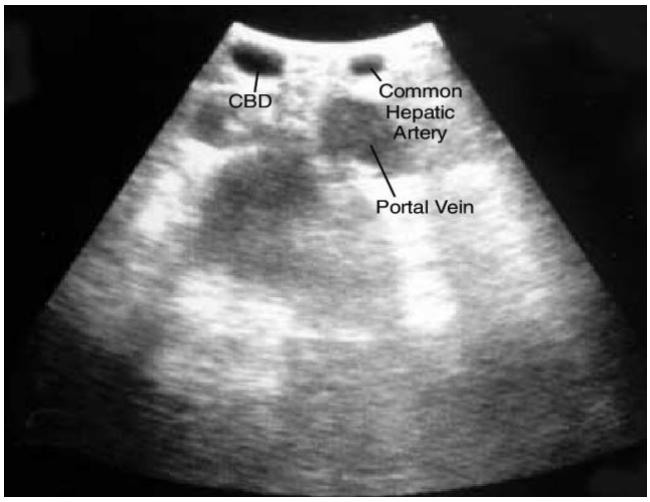

Figure 7 IOU of hepatoduodenal ligament reveal Micky mouse appearance[32].

Intra-operative cholangiograms (IOC) accurately detect CBD stones with a sensitivity of 59% to 100% and specificity of 93% to 100%. It might also reduce or at least assist with early diagnosis of CBD injuries during cholecystectomy. IOC can be performed during open or laparoscopic cholecystectomy. The advantage of IOC is that the surgeon can deal with findings intra-operatively by flushing the duct, extract stones with a Fogarty's catheter, perform a CBD exploration, or ERCP post-operatively. IOC both maximise and minimise the use of ERCP[33–35].

The ongoing debate is if IOC should be performed routinely or selectively, with no clear consensus which is superior. Most surgeons perform IOC selectively as it is time-consuming and false-positive results can lead to unnecessary CBD exploration[36]. Selective IOC is performed in the intermediate group as described earlier.

The routine IOC is performed in every case of laparoscopic cholecystectomy regardless of the pre-operative LFTs or U/S. In the past IOC was used in open cholecystectomy as described by Mirizzi[37]. Routine IOC aims to reduce a bile duct injury by demonstrating the bile duct anatomy and reduce retained CBD stones. Some reports find the incidence of CBD injury to be 0.1-0.3%[38] but others report much higher up to 1.4%[39]. The other advantage of a routine IOC is to keep surgeons exposed to the procedure. In addition, the use of a routine IOC can detect a CBD injury, but not reduce the risk[40]. Although, some studies find that it can reduce

the CBD injury in up to 70%[39]. The additional time consumed by an IOC (16 minuntes) and the false-positive result of CBD stones made the routine use of IOC a debatable subject[41]. Additionally, in eight randomized trials no one demonstrated a clear benefit of routine IOC to reduce retained stones[42].

Surgeons tend to move towards a selective use of IOC depending on the risk factors as described in table 1. Hereby aiming to reduce the time of the operations, decrease false-positive results and to minimize the handling of the biliary system. The selection of the patients depends on the ASGE guideline 2019[43]. A history of jaundice, raised liver enzymes and U/S abnormality select patients to the intermediate-risk group for which selective use of the IOC is recommended[44].

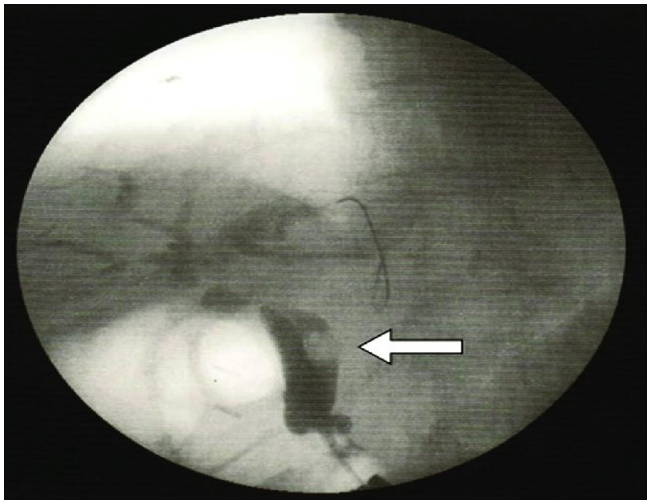

Figure 8 IOC demonstrating a 10-mm CBD stone (arrow)[45].

Risk assessment

The assessment for CBD stones must use the least invasive and cost-effective investigation to confirm or exclude CBD stones. The guidelines propose dividing patients into three groups according to the risk of choledocholithiasis (2019 guidelines)[43]. In other words, risk stratification of the likelihood of having a CBD stone.

Table 1: Risk assessment of CBD stones[43].

High-risk groups	At least one very strong predictor and/or both strong predictors
Intermediate-risk groups	One strong predictor and/or at least one moderate predictor
Low-risk groups	No predictors

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Table 2: Patient stratified on CBD stones[43]

Very strong predictors	The presence of a common bile duct stone on transabdominal ultrasound Clinical acute cholangitis, A serum bilirubin greater than 4 mg/DL (68 micromoles/L)
Strong predictors	A dilated common bile duct on ultrasound (more than 6 mm in a patient with gallbladder in situ) A serum bilirubin of 1.8 to 4 mg/DL (31 to 68 micromoles/L)
Moderate predictors	Abnormal liver biochemical test other than bilirubin Age older than 55 years Clinical gallstone pancreatitis

Using the above predictors, patients are stratified in a high-risk, intermediate-risk and low-risk group.

Those who are categorised into the high-risk groups are estimated to have more than 50% likelihood of choledocholithiasis[43]. For these patients, the initial management is ERCP to treat any CBD stones before cholecystectomy[46].

The intermediate-risk group is estimated to have CBD stones between 10-50% of the cases[47]. This group need further evaluation for CBD stones. The incidence does not warrant the risk-benefit of doing a pre-operative ERCP. The biliary tree can be imaged with an MRCP, IOC or EUS. The decision depends on multiple factors such as cost, patient factors, availability of MRI/EUS and suspicion for small stones. MRCP is one option in the intermediate-risk group and if it is positive, proceed with an ERCP before cholecystectomy. EUS is further option, but equipment and skills are less available. It is also procedural with the associated risk although less than ERCP. There is no difference between IOC and EUS regarding complications, conversion to open or mortality. The only difference is hospital stay with the EUS group slightly longer than for the IOC group[48].

Low-risk patients are estimated to have CBD stones in less than 10% and for this group cholecystectomy can be done without additional pre-operative biliary tree imaging[43].

Management

It is generally accepted that patients with choledocholithiasis should have the biliary system cleared of stones. This can be achieved via surgery (open or laparoscopy) or endoscopically[49,50]. As the majority of choledocholithiasis is the result of the migration of cholelithiasis to the common bile duct, part of the management is a cholecystectomy as a one-step or two steps procedure[43]. A meta-analysis of 16 published randomised trials evaluated which strategy is superior and did not show any significant differences in morbidity or mortality[51]. The incidence of a retained CBD stone was significantly less in open CBD

exploration compare to the two-step procedure. Management by laparoscopic CBD exploration is associated with a shorter hospital stay[52,53].

A one-stage procedure is to perform an ERCP intraoperatively with a laparoscopic cholecystectomy. As seen in the literature it needs two teams to perform the procedure. Also, it requires a well-equipped theatre. A one stage procedure is associated with less pancreatitis: 0.6% comparing to 4.4% to the two-stage procedure. Also, the overall morbidity is higher in two-stage procedure 11% comparing to one stage procedure 6%. The one-stage procedure has a shorter hospital stay where the two-stage procedure needs two admissions and anaesthetics. The trails concluded that the one-stage procedure is better financial value than the two-stage procedure[54]

Endoscopic management

ERCP was first performed in 1974[55] and since then it has become the most broadly practised technique for diagnosing and management of choledocholithiasis[56].

The procedure involves the identification of the papilla of Vater, then cannulation of the duct to perform a biliary sphincterotomy followed by extraction of the CBD stones by balloon or basket. The complications can vary widely according to the indication rather than the age or comorbidity. The morbidity is 5% to 9.8%, and the mortality of 0.3 to 2.3%[46]. The complications include bleeding, perforation and acute pancreatitis[57,58]. The timing of the procedure can be before surgery, during (rendezvous technique) or after the cholecystectomy.

Pre-operative endoscopic management is indicated in the high-risk group (Table 2), followed by cholecystectomy after clearing the common bile duct. Intra-operative endoscopic management (rendezvous technique) or one-step procedure could be a very eloquent solution. However, it is rarely performed in developing countries where it needs another team with ERCP hardware and disposables in the operating room when it is indicated if the IOC demonstrates CBD stones[59]. Post-operative endoscopic management or a two-step procedure is indicated when a positive IOC needs an ERCP to clear the CBD, which is commonly performed in our setting. Failure to achieve post-operative endoscopic clearance of the duct can necessitate a second operation[60,61]. This strategy should not be followed if the stones are clearly not amenable to endoscopic treatment as judged on the IOC. Large stones

or a big stone burden should be considered for immediate CBD exploration, although they are likely to have been diagnosed pre-operative.

Endoscopic papillary balloon dilatation (EPBD) was introduced to minimise the sphincter damage and assist in the delivery of large stones. It is performed with a minimal sphincterotomy and has been used for high bleeding risk patients or those who have difficult anatomy to perform a full sphincterotomy e.g. periampullary diverticulum. After biliary cannulation and limited sphincterotomy, a dilatation balloon is advanced over the guidewire and inflated. The balloon sizes vary from 8-20 mm and the size of the duct on initial cholangiogram should be used as a guide in order not to rupture the duct. The advantage of minimal sphincterotomy and balloon dilatation has decreased the risk of bleeding and lower infection rate, but the disadvantage is a higher recurrence rate[62–64].

Endoscopic mechanical lithotripsy (EML) is a strategy for difficult common bile duct stones that cannot be extracted by Dormia basket or balloon catheter. The lithotripsor consists of a hardwire basket with a metal spiral sheet. When the stone is captured in the basket and pulled back to the rigid sheath, the stone can be crushed by an out of scope lithotripsor[65]. This technique has been updated by a through the scope lithotriptor, which could reach 80% to 90% clearance of the common bile duct[66]. Failure of mechanical lithotripsy could be when the common bile duct stone is too big to be captured by the basket or when the stone is impacted in the distal common bile duct[49]. A complication can occur when it is not possible to crush a captured stone with the device stuck in the duct which will dictate surgical removal.

Endoscopic electrohydraulic lithotripsy (EEL) was first used in 1975 through a T-tube tract under fluoroscopy guidance[67]. Modern-day use would be with a through the scope cholangioscope (SPYGLASS system) where the duodenoscope and cholangioscope (spyscope) are controlled by the same endoscopist. By performing electrohydraulic lithotripsy using a 3-Fr probe after cannulation of the common bile duct, a success rate ranging from 74% to 98% was reported[68].

Endoscopic laser lithotripsy (ELL) is used under direct vision through a cholangioscope (SPYGLASS) to avoid heat-induced injury to the biliary system. Clearance of the common bile duct can be achieved through this technique between 93% to 97% of the times[69].

SURGICAL MANAGEMENT

Open procedures were the standard of care for clearing of CBD stones in the 1980s. It is performed through an open CBD exploration or rarely duodenotomy plus sphincterotomy. Nowadays, it considered the last resort in difficult CBD stones. Still, a recent study showed it is superior to ERCP for clearing CBD stones in 96% to 98% of cases with no significant differences in morbidity (20% vs 19%) and mortality (1% vs 3%)[51].

Since the laparoscopic era, CBD exploration can be performed this way. In expert hands, it is as useful as ERCP for clearing the common bile duct. However, it takes longer (300-358min)[70] than for a simple cholecystectomy. When one reaches a critical view of safety and a CBD stone is identified by IOC or intra-operative U/S, the first attempt could be to irrigate the CBD through the cystic duct aiming to clear the CBD. If it fails a choledochotomy performed along the CBD to allow introducing a choledochoscope to extract the stones by Dormia basket or balloon extraction[5,61].

Intra-operative cholangiogram procedure

The most common indication for IOC is for the diagnosis of CBD stones. Other indications such as clarification of biliary anatomy to facilitate the dissection or to prevent biliary injuries might be used. Moreover, it can identify other abnormalities like biliary leaks or strictures. There are several techniques described to perform IOC. The most common are Kumar (through the gallbladder) and Olsen (through the cystic duct) cannulation techniques. There is no one proven to be superior to another, so surgeons can use either of them depends on which is preferred[71].

The additional equipment needed to perform an IOC includes: on table fluoroscopy, commercial pre-packed cholangiogram kit which consists of a catheter or a cannula, a syringe, introducer needle/sheath, a 3-way stopcock (figure 11), and contrast medium. In limited

resources institutions, the cholangiogram can be done by a urethral catheter (size: 3 Fr) and reusable cholangiogram clamp instrument (Olsen's forceps)[72].

During laparoscopic cholecystectomy, after achieving the critical view of safety, a clip is applied to the proximal cystic duct to avoid spillage of bile and stones from the gallbladder. A small cystic ductotomy can be made (the Olsen method) to facilitate the catheter to advance into the biliary tree by using an Olsen clamp (figure 10). If a commercial set is used, a small stab incision in the upper right quadrant in a place of convenience can be made to pass the cholangiogram catheter percutaneously into the cystic ductotomy. The catheter should be temporarily fixed by inflating the balloon, cystic duct holding device or umbrella mechanism. If the critical view of safety cannot be achieved, a cholangiogram needle is inserted into Hartmann's pouch of the gallbladder using a Kumar clamp to secure the needle (The Kumar method as in figure 9).

After succeeding with access to the biliary tree, good flow can be confirmed by flushing with saline and this also avoids contrast spillage, which could obscure the fluoroscopy image. If the biliary tree is dilated one could dilute the contrast 50/50 with saline to not miss small filling defects in dense contrast. Great care should be given to avoid injection of air bubbles which could lead to a false positive study. When screening, request apnoea form the anaesthetist and place the patient in right tilt Trendelenburg position to obtain the best quality image of the hepatic biliary system. Care should be taken to identify any anatomical variation. Change patient position to anti-Trendelenburg to visualize and dynamic timing of the contrast going into the duodenum.

Additionally, this manoeuvre facilitates the air bubbles to move superiorly. Air bubbles can also be recognised from actual filling defect by them joining each other. If there is a delay in emptying, glucagon 1-2 mg intravenous can be administered to relax the sphincter of Oddi. If a delay persists in emptying of the biliary system into the duodenum, it could be a distal obstructed stone and one should be vigilant to look for a cresent[64]. In theory, a complete cut off should raise the suspicion of a CBD injury.

If there is difficulty to insert a cholangiogram catheter caused by a stone in the cystic duct, the surgeon can perform a milking manoeuvre to remove it through cystic duct incision. If

milking the stone out is unsuccessful or the cystic duct has a sharp angle, a guidewire can be inserted following with catheter sheet over it. Avoid overfilling of the biliary tree with contrast solution as a small stone can be missed. A filling defect can represent an intraluminal tumour, air bubbles or most likely stones. As mentioned before, care should be taken by flushing with saline before and after the injection of the contrast and screening from deferent angles while moving the patient can help to differentiate between the filling defects[71–73].

A positive IOC is depended on biliary dilatation with a filling defect. Failure of passage of the dye with other signs also should be noticed like a stricture or a leak but it does not reflect a positive IOC. The interpretation is different from surgeon to another or from surgeon to radiologists so that makes the false-negative of 1.5% and false-positive IOC of 2.0%. There is a report comparing surgeon versus radiological interpretation of a IOC which demonstrates a substantial difference between both teams with poor interpretation by surgeons. However, that is not reflect the clinical outcome [74,75].

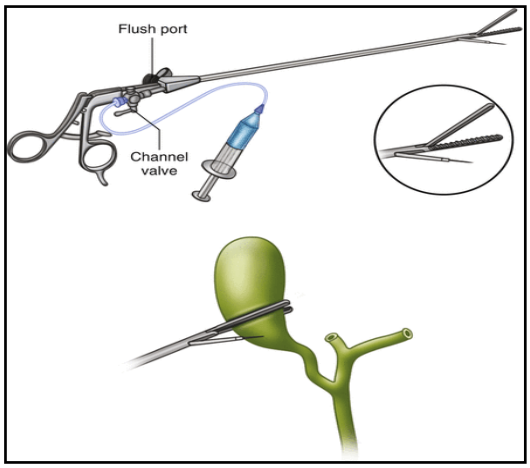

Figure 9 Kumar method [76]

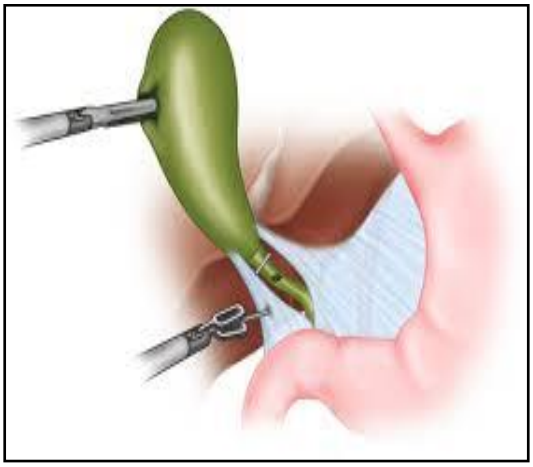
Figure 10 Olsen method [76]

Figure 11 commercial cholangiogram kit.

Conclusion

Figure 12 summarizes a diagnostic and treatment algorithm for suspected CBD stones. These modalities are not always readily available and practical in the South African health care setting. There is a paucity of data on the local disease profile and treatment. However, despite deficit studies on internal management of choledocholithiasis, it should be noted that a retained CBD stone post laparoscopic cholecystectomy may lead to serious complications. Therefore, patients should be categorised according to the prediction of having a CBD stone to minimise the sequences of a missed CBD stone. In our setting a IOC is a suitable choice for diagnosing and further treating of the intermediate-risk group of CBD stone. Furthermore, IOC does not cost much and has fewer complications comparing with other modalities.

Summary of the management

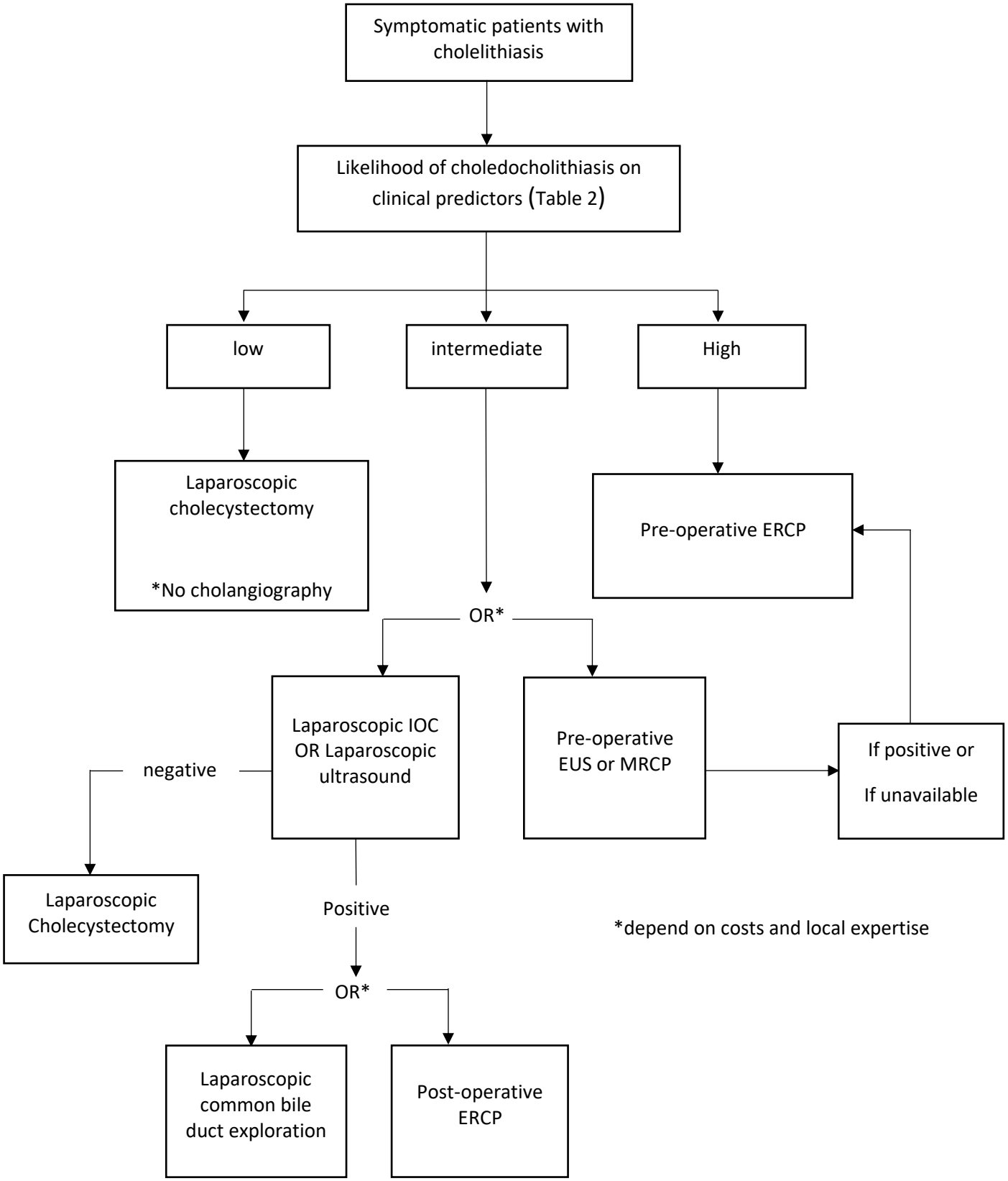

Figure 12 The American Society for Gastroenterology Endoscopy algorithm for the management of patients with symptomatic cholelithiasis based on the degree of probability for choledocholithiasis[43].

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Part C - Publication ready original manuscript

Which pre-operative findings translate to a positive intra-operative cholangiogram?

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Running head: Intraoperative cholangiogram**.** Choledocholithiasis.

Keywords: choledocholithiasis, cholecystectomy, intraoperative cholangiogram (IOC).

Abstract

Background: The most common investigations used in the pre-operative diagnosis of choledocholithiasis are ultrasound and liver function tests (LFTs). These modalities have a low sensitivity for detecting common bile duct stones amongst the intermediate-risk groups.

Aim: Identify pre-operative findings which predict choledocholithiasis in intermediate-risk groups. Describe the implications of a positive intra-operative cholangiogram (IOC).

Method: A retrospective study of all consecutive laparoscopic cholecystectomies with IOC performed. Data were collected over two years between 1st January 2015 and 31st December 2016. Standard demographic variables, preoperative symptoms, LFTs, IOC findings, abdomen ultrasound, and postoperative symptoms were included.

Results: 23 cases were planned for IOC. The median age was 41 years. Seventeen cases were females. Indications were 12 biliary colic, eight gallstone pancreatitis, two cases of acute cholecystitis, and one case was for ascending cholangitis. Four cases had a positive IOC, and in this group, the median age was 44.5 years with one male. The mean common bile duct diameter was 6.5 mm. Two patients had biliary colic, one patient gallstone pancreatitis and one acute cholecystitis. One patient had a history of jaundice, and all four cases had elevated GGT above 40 mmol/l, three cases had ALP above 98 mmol/l. Post-operative, out of 23 cases, five cases had an ERCP, repeated ultrasound in three cases, persistence symptoms in four cases.

Conclusions: GGT was the strongest predictor of choledocholithiasis. A normal GGT seems to be quite good at ruling out CBD stones. ALP was less accurate. Gallstone pancreatitis is not a good predictor, but it is importance to exclude choledocholithiasis before/during cholecystectomy. There is no relation between the IOC and persistent symptoms.

Introduction

In the 30-year era of laparoscopic cholecystectomy, two questions have not clearly been answered in the intermediate-risk groups[1,2] of choledocholithiasis. First, the most cost-effectiveness modality to identify CBD stones, and secondly if CBD stone found how to deal with it?[3]

IOC is one modality for detecting CBD stones, but in published literature, there is little benefit in performing IOC routinely[4]. Selective IOC is the most common strategy, but no data support its benefit or which tests should be selected for which indication[5,6]. The indication for selective IOC would be abnormal liver enzymes and/or dilated biliary system on pre-operative ultrasound. Accordingly, the patients would be categorized as an intermediate-risk group for choledocholithiasis[7]. Cases with mild gallstone pancreatitis would also fall into this group. Jaundice patients would be in a high-risk group and thus justify pre-operative endoscopic retrograde cholangiopancreaticogram (ERCP), which reflect our current practice.

There is still an ongoing debate if IOC is cost-effective and reliability either as a routine or selective modality[8–11]. In routine use, the systemic review of eight randomised trials showed no benefit in the prevention of a retained CBD stone[4]. IOC advantages are relatively low-cost and it does not require advanced laparoscopic skills, although you need the availability of mobile fluoroscopy. IOC has 59%-100% sensitivity and 93% -100% specificity to detect CBD stones[12]. The disadvantages of IOC are a longer operation time by 16 minutes, technical difficulty in acute inflammation and anatomical variation like a short cystic duct[13]. Furthermore, it could potentially lead to a CBD injury or false-positive results which can lead to unnecessary CBD explorations or invasive procedures (postoperative ERCP). Few studies are evaluating the sensitivity or specificity of pre-operative tests in detecting CBD stone among intermediate-risk groups[2,5,14,15].

The other unresolved issue is the treatment algorithm when detecting a filling defect on IOC. Options are performing an immediate operative CBD exploration, post-operative ERCP or

clinical observation and imaging follow up. Our current practice is to perform a post-operative ERCP. CBD exploration is reserved for failed endoscopic management.

As clearly seen in the literature, there are no universal guidelines for the use of IOC[7,16–18]. There are two role-players in MRCP and endoscopic ultrasound for the pre-operative imaging of the bile duct, but in a limited resource environment, this cannot be accessed routinely. Also, an efficient, cost-effective approach that avoids unnecessary investigations and unnecessary risk for the patient. Our study would correlate if intermediate-risk groups warrant any further intervention of the CBD.

Materials and methods

A retrospective analysis of a prospectively maintained database for all patients who underwent a cholecystectomy with intraoperative cholangiogram at Groote Schuur Hospital in the Acute Care Surgery and Hepato-Pancreato-Biliary units between 1st of January 2015 and 31st December 2016. Standard demographic variables including age and gender were documented as well as pre-operative symptoms, indications of cholecystectomy (biliary colic, gallstone pancreatitis, ascending cholangitis, and acute cholecystitis) were mentioned, preoperative LFTs (bilirubin, GGT, ALP, AST and ALT), IOC findings, post-operative abdomen ultrasound (dilated CBD), MRCP, ERCP, and persistence symptoms were detailed. The data was collected from patients' hospital files, operation notes, images on GSH pacs and blood results on NHLS online tool.

Data was exported to Stata version 13.0 (Stata Corp., College Station, TX, USA) for analysis. For descriptive statistics, categorical values were summarised as frequencies and percentages. The chi-square test (or Fisher’s exact test) were used to compare categorical variables by the positivity of IOC. Continuous variables (all non-normally distributed per Shapiro-Wilk test) were summarised using medians with interquartile range. The Kruskal-Wallis test was used to compare continuous variables by IOC positivity.

The required data collection and analysis of this study was approved by the Faculty of Health Sciences Human Research Ethics Committee of the University of Cape Town (HREC 712/2018).

Results

During the two-year study period, a total of 237 laparoscopic cholecystectomies were performed. In this cohort, 23/237 (9.7%) patients fell into the intermediate-risk group requiring an IOC. 17/23 (73.4%) were female and the indications for the cholecystectomy were biliary colic (12/23; 52.2%), gallstone pancreatitis (8/23; 34.9%), acute cholecystitis presentation in two cases, and one case with ascending cholangitis. Twenty-one patients had elevated GGT more than 40 mmol/l, and seven patients had ALP less than 98 mmol/l, eight patients had an ALP more than 98 mmol/l and less than 200 mmol/l, eight patients had an ALP above 200 mmol/l, no patient had elevated serum bilirubin as this is considered a high-risk group patient which would be managed by pre-operatively ERCP. The results are summarised in Table 3.

In this study (4/23 or 17.4%) of the intermediate-risk group had choledocholithiasis. (figure 15). The four cases who had positive findings on IOC: the median age was 44.5 years (36-58), one case was a male (25%), CBD diameter on ultrasound was between 6-7 mm (median 6.5mm). The indications for cholecystectomy in this subgroup were two cases with biliary colic, one case of acute cholecystitis and one case of ascending cholangitis. One case had a history of jaundice. Pre-operative LFTs, four cases had raised GGT more than 40 mmol/l, and one case had ALP less than 98 and 3 cases ALP was between 98 and 200 mmol/l. two cases had AST more than 35 and three cases had ALT more than 35 mmol/l. Summarised in Tables 3-4.

Postoperatively; four cases who had a positive IOC had a post-operative ERCP for stones extraction. No case had a CBD exploration, out of 23 cases three had a repeat ultrasound, no one had an MRCP, four out of 23 had persistent symptoms postoperatively. Summarised in Table 5.

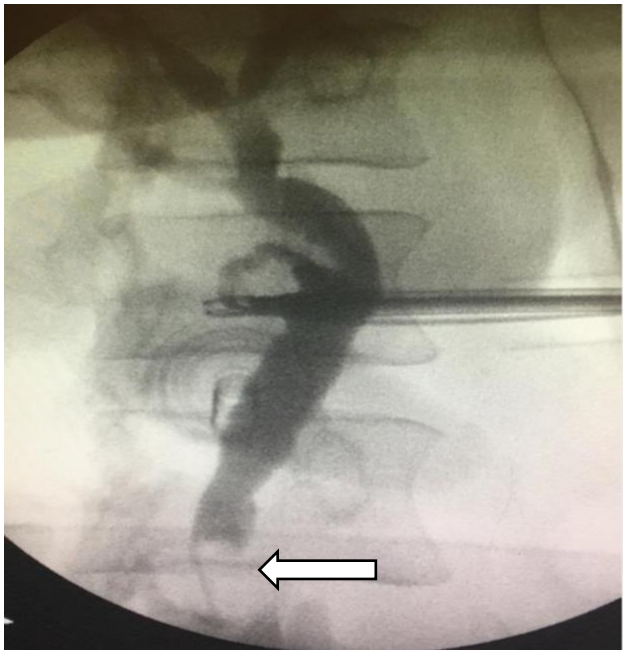

Figure 93 Case number 16 showed a filling defect in CBD (arrow).

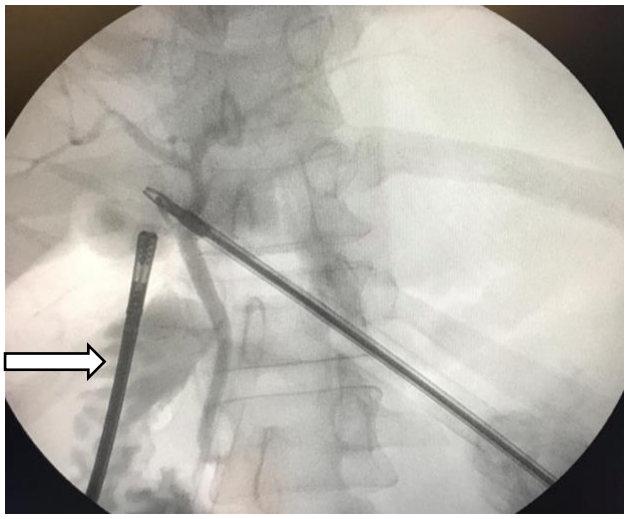

Figure 14 Case number 5 no filling defect. the contrast in the duodenum (arrow).

Table 3: Characteristics of the study participants

Characteristic	Summary (n=23)	Positive IOC (n=4)	Negative IOC (n=15)
Demographic			
Age (years), median (IQR)	41.0 (31-55)	44.5 (36-58)	41 (29-59)
Male Sex, n (%)	6 (26.1%)	1 (25.0%)	5 (33.3%)
Ultrasound			
CBD size (mm), median (IQR)	6.0 (6-7)	6.5 (6-7)	6 (6-9)
Indication for cholecystectomy			
Biliary colic	12 (57.2%)	2 (50.0%)	7 (44.7%)
Gallstone pancreatitis, n (%)	8 (34.8%)	1 (25.0%)	6 (40.0%)
Acute cholecystitis, n (%)	2 (8.7%)	1 (25.0%)	1 (6.7%)
Ascending cholangitis, n (%)	1 (4.4%)	0 (0.0%)	1 (6.7%)
History of Jaundiced, n (%)	8 (34.8%)	1 (25.0%)	5 (33.3%)
Laboratory			
AST > 35, n (%)	8 (34.8%)	2 (50.0%)	4 (26.7%)
ALT > 35, n (%)	11 (47.8%)	3 (75.0%)	9 (60.0%)
GGT >40, n (%)	21 (91.3%)	4 (100.0%)	13 (86.7%)
GGT, n (%)			
<40	2 (8.7%)	0 (0.0%)	2 (13.3%)
40 to <150	8 (34.8%)	1 (25.0%)	5 (33.3%)
150 to <400	8 (34.8%)	2 (50.0%)	4 (26.7%)
>400	5 (21.8%)	1 (25.0%)	4 (26.7%)
ALP >98, n (%)	16 (69.6%)	3 (75.0%)	9 (60.0%)
ALP, n (%)			
<98	7 (30.4%)	1 (25.0%)	6 (40.0%)
98 to <200	8 (34.8%)	3 (75.0%)	2 (13.3%)
>200	8 (34.8%)	0 (0.0%)	7 (46.7%)
Raised WCC (>11), n (%)	4 (17.4%)	0 (0.0%)	4 (26.7%)

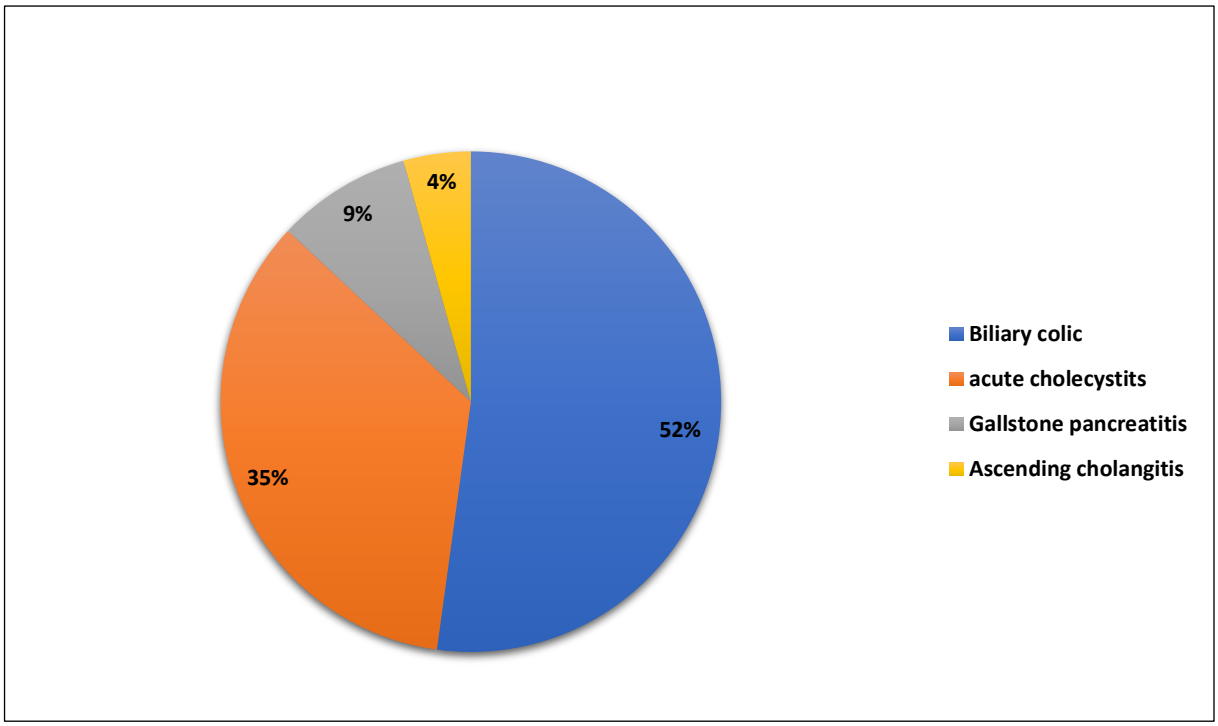

Figure 15 Indication for cholecystectomy in the patients requiring IOC

Table 4: Correlates of a positive IOC

Characteristic	Crude OR (95%CI)
Age (years)	1.02 (0.95-1.10)
CBD size (mm)	0.72 (0.19-1.54)
Male sex	0.68 (0.01-11.40)
Biliary colic	1.14 (0.07-19.68)
History of jaundice	0.68 (0.01-11.40)
GGT>40	0.66 (0.05-inf)
ALP>98	1.94 (0.12-122.22)
ALT>35	1.14 (0.07-19.68)
AST>35	2.59 (0.14-48.00)
Raised WCC>11	0.61 (0.00-6.31)

Table 5: Post-operative characteristics of the study participants

Characteristic	Summary
Common bile duct exploration, n (%)	0 (0%)
Post – ERCP, n (%)	4 (17.4%)
Repeat ultrasonography, n (%)	3 (13.0%)
New MRCP, n (%)	0 (0%)
Repeat surgery, n (%)	0 (0%)
Persistent symptoms, n (%)	4 (17.4%)

Discussion

This study aimed to identify the most predictive test for CBD stones pre-cholecystectomy, but another interested finding in this study was: 23 of 237 patients in the Groote Schuur practice fell into the intermediate group and four of these had proven choledocholithiasis. In the literature, the most commonly used are ultrasound, history of jaundice, biliary pancreatitis, CBD dilatation, and pre-operative LFT's to estimate the risk of having CBD stones[14,15]. We found that the four cases who had positive IOC's had elevated GGT of more than 40 mmol/l, which was not surprising as the 23 patients who were planned to have IOC, 21 had raised GGT levels. In our analysis, a raised ALP of more than 98 mmol/l was found in 75% which correlates with the literature of 79.5 %[14]. All our patient's bilirubin was within the normal range or slightly raised. As seen in universal guidelines significantly increased bilirubin is considered to be in the high-risk group for which an ERCP is indicated pre-operatively. AST and ALT more than 35 mmol/l occurred in 50% and 75%, consequently within our study analysis, the sensitivity is 63% and 71.6%[2]. In this study, gallstone pancreatitis did not predict the presence of CBD stones, however, it is beneficial to exclude CBD stones by IOC or pre-operatively MRCP, as it may lead to critical consequences[7].

There is very little data from Africa about IOC to compare with our clinical practice and outcomes. One study from Egypt[19] which attempted to define the role of IOC in laparoscopic cholecystectomy showed pre-operative ALP elevated in 82% which is in keeping with our analysis of 75% above 98 mmol/l. However, the CBD was dilated in 48% wherein our series it

was 17% more than 8 mm. Interesting, all four cases who had a positive filling defect had a normal CBD diameter. As in the literature[20,21], the CBD diameter on abdominal ultrasound has low sensitivity for prediction of CBD stones. They concluded that the value of IOC is high in comparison to the minimal complications. Moreover, it has higher diagnostic accuracy than MRCP; it saved another admission for the patient who underwent intra-operative evaluation [19]. There is no data from South Africa regarding IOC as it is not commonly used in South African institutions where they rely mainly on ERCP for managing CBD stones as a diagnostic and therapeutic procedure instead of IOC[22].

The retrospective nature is a serious limitation of this study. Also considering the shallow sample size (n=23), the study has low power to detect differences. However, it suggests where differences could be rather than affirmatively showing these differences. For example, it suggests those with positive IOC's are more likely to be of higher age which is somehow significant. In the published guidelines the age above 55 years is categorised as a moderate predictor for choledocholithiasis, but one cannot be affirmative about this finding since the statistical power is low.

One of the recommendations from this study is the need to conduct ongoing prospective research. Establishing a gallstone registry might even contribute to the standardisation of care. As we practice in limited-resource environments, institutions cannot routinely offer reliable, accurate tools for identification of choledocholithiasis such as MRCP, intra-operative U/S or even ERCP. Pre-operative predicted modules such as LFT and IOC selectively as indicated are cost-effective and reduce the incidence of retained CBD stones post-cholecystectomy.

Conclusion

A normal GGT has good negative predictive value. In a limited resources facility, IOC is cost-effective to confirm or exclude choledocholithiasis with minimal complications.

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Part D - Supporting documents

List of abbreviations

ALP	Alkaline phosphatase
ALT	Alanine transaminase
AST	Aspartate transaminase
CBD	Common bile duct
EEL	Endoscopic electrohydraulic lithotripsy
ELL	Endoscopic laser lithotripsy
EML	Endoscopic mechanical lithotripsy
EPBD	Endoscopic papillary balloon dilatation
ERCP	Endoscopic retrograde cholangiopancreatogram
EUS	Endoscopic ultrasound
FBC	Full blood count
Fr	French gauge
GB	Gallbladder
GGT	Gamma-glutamyltransferase
IOC	Intra-operative cholangiogram
IOU	Intra-operative ultrasound
LFT	Liver function test
mg	Milligram
mm	Millimetre
mmol/l	Millimole per litre
MRCP	Magnetic resonance cholangiopancreatogram
SAGES	Society of American Gastrointestinal and Endoscopic Surgeon
U/E	Urea and electrolytes
U/S	Ultrasound

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Authorship

Named authors must consent to publication. Authorship should be based on substantial contribution to:

(i) conception, design, analysis and interpretation of data;

(ii) drafting or critical revision for important intellectual content; and

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Provide evidence of Research Ethics Committee approval of the research where relevant.

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References to ethnic classification must indicate the rationale for this.

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Shorter items are more likely to be accepted for publication, owing to space constraints and reader preferences.

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following recommended headings: Background, Objectives, Methods, Results, and Conclusion.

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Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.

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Journal references: Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. Stat Med 1998;289(1):350-355. [http://dx.doi.org/10.1000/hgjr.182] [PMID: 2764753]

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Dr C. Kloppers
DIVISION OF GENERAL SURGERY

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Dear Dr Kloppers,

RESEARCH PROJECT: Predictive Model Correlating Pre-Operative Findings With Intra-Operative Cholangiogram Results (MMed. Dr Mohamed Elmusbahi)

Your recent letter to the hospital refers.

You are granted permission to proceed with your research, which is valid until **30 November 2019.**

Please note the following:

a) Your research may not interfere with normal patient care.
b) Hospital staff may not be asked to assist with the research.
c) No additional costs to the hospital should be incurred i.e. Lab, consumables or stationary. **If access to TRACK Care/NHLS is required, kindly attach our letter of approval to the application form.**
d) **No patient folders may be removed from the premises or be inaccessible.**
e) Please provide the research assistant/field worker with a copy of this letter as verification of approval.
f) Confidentiality must always be maintained .
g) Should you at any time require photographs of your subjects, please obtain the necessary indemnity forms from our Public Relations Office (E45 OMB or ext. 2187/2188).
h) Should you require additional research time beyond the stipulated expiry date, please apply for an extension.
i) Please discuss the study with the HOD before commencing.
j) Please introduce yourself to the person in charge of an area before commencing.
k) On completion of your research, please forward any recommendations/findings that can be beneficial to use to take further action that may inform redevelopment of future policy / review guidelines.
l) Kindly submit a copy of the publication or report to this office on completion of the research.
m) At no time should any posters encouraging patients to partake in research, be displayed within a clinical area.

I would like to wish you every success with the project.

Yours sincerely

Signature Removed

DR BERNADETTE EICK
CHIEF OPERATIONAL OFFICER
Date: 25 September 2019

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09 November 2018

HREC REF: 712/2018

Dr C Kloppers
Division of General Surgery
E23 GIT Unit
NGSH

Dear Dr Kloppers

PROJECT TITLE: PREDICTIVE MODEL CORRELATING PRE-OPERATIVE FINDINGS WITH INTRA-OPERATIVE CHOLANGIOGRAM RESULTS (MMED Candidate - Dr M Elmusbahi)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 November 2019.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

We acknowledge that the student: Dr Mohamed Elmusbahi will also be involved in this study.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

Signature Removed

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938