Evaluation of predictors for choledocholithiasis and assessment of outcomes after treatment.

A historical cohort study

Dissertation submitted to

The Tamil Nadu Dr. MGR Medical University

In partial fulfilment for the

Degree of M.S. Branch I General Surgery

April 2014

CERTIFICATE

This is to certify that the dissertation titled '**Evaluation of predictors for choledocholithiasis and assessment of outcomes after treatment, a historical cohort study**' is the bonafide work of **Dr. Sam Joel**, in fulfilment of the rules and regulations for the **M.S., Branch 1, General Surgery** Examination of **The Tamil Nadu Dr. M.G.R. University**, to be held in April, 2014.

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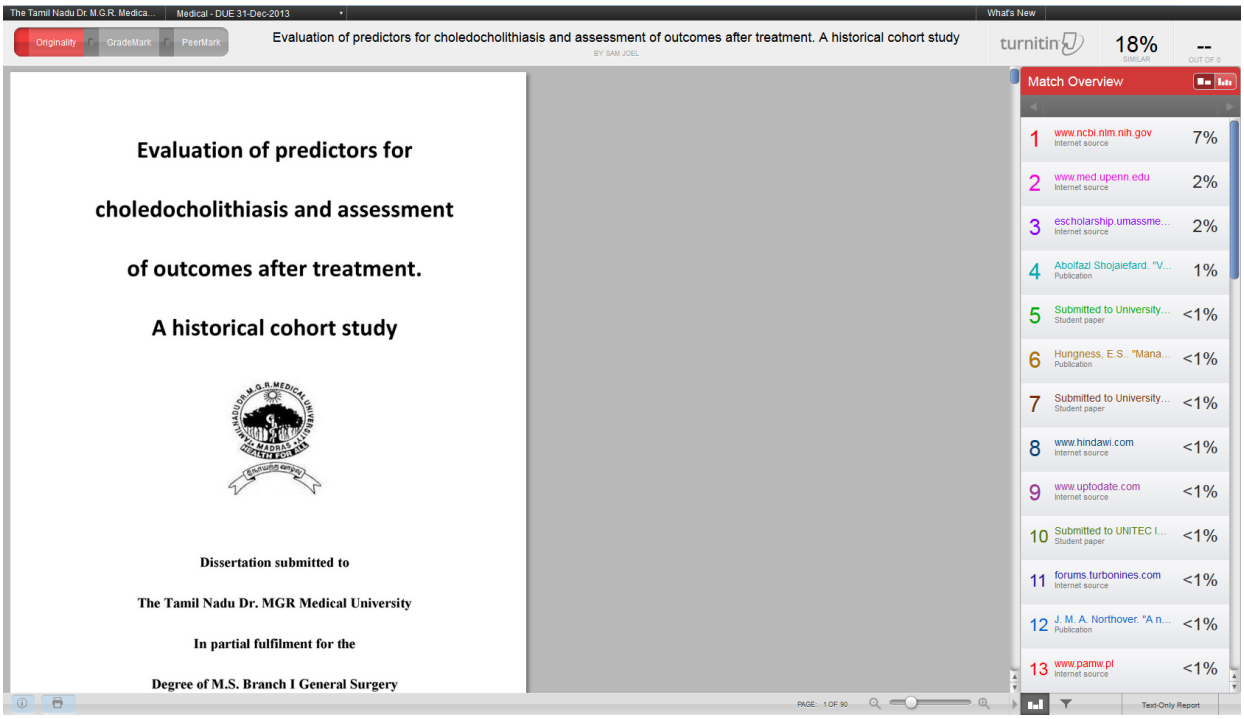

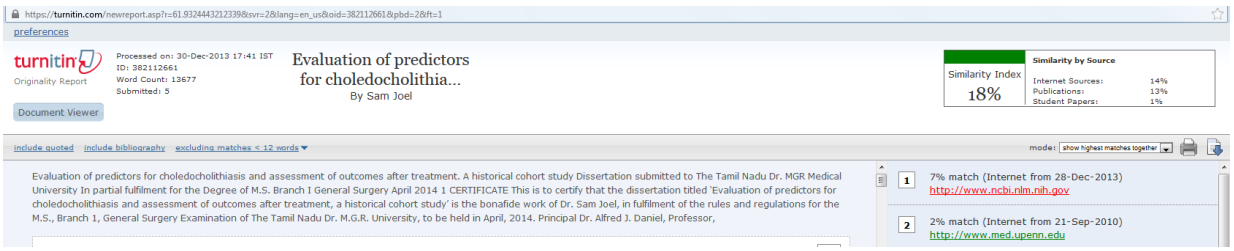

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I enclose the following documents:-

1. Institutional Review Board approval
2. Agreement

Could you please sign the agreement and send it to Dr. Nihal Thomas, Addl. Vice Principal (Research), so that the grant money can be released.

With best wishes,

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Secretary (Ethics Committee)
Institutional Review Board

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CONTENTS

ABSTRACT

Title of the Abstract:

Evaluation of predictors for choledocholithiasis (common bile duct stones) and assessment of outcomes after treatment

Department: Department of General Surgery, Christian Medical College, Vellore

Name of the candidate: Dr. Sam Joel M.

Degree and Subject: Master of Surgery – General Surgery

Name of the Guide: Dr. Philip Joseph

Objectives:

1. To study the clinical, laboratory and radiological findings of patients diagnosed with common bile duct stones.

2. To study the current practice of managing this condition in our tertiary care hospital (Christian Medical College and Hospital).

3. To obtain data of a one year follow up of these patients who had undergone treatment for choledocholithiasis.

Background:

Common bile duct (CBD) stones are seen in 5% to 10% of those undergoing cholecystectomy. Missed CBD stones pose a risk of recurrent symptoms of

abdominal pain, pancreatitis, and cholangitis unless identified at presentation. Therefore identifying the key predictors at presentation is of great value.

Methods:

Cohort of patients diagnosed with choledocholithiasis who presented to the outpatient clinic of Hepatic Pancreatic and Biliary Surgery, General Surgery and Gastroenterology departments at Christian Medical College, Vellore from July 2008 to June 2012 were included in the study, and one year follow up data was also collected. The presenting history, clinical examination, laboratory tests and radiological imaging in the patients were recorded in the performa.

Results:

The management practice in this tertiary care centre along with the various relevant clinical, biochemical and imaging parameters were identified. Abdominal pain was the common complaint (76%). Jaundice was a significant predictor for failure of ERCP. Abdominal ultrasonography commonly showed CBD dilation (85.4%) and intrahepatic biliary radical dilatation. MRI was the most sensitive to demonstrate CBD stone (86.6%). ERCP was the primary modality of treatment. CBD exploration was the treatment of choice in case of failed ERCP and stone extraction. There were recurrent CBD stones in 5% of the follow-up population.

Discussion:

The most common clinical presentation of choledocholithiasis was abdominal pain. The presence of a dilated common bile duct of above 10mm associated with

intrahepatic biliary dilatation was the commonest initial radiological finding. Abdominal ultrasound was an effective modality to pick up common bile duct stones but MRI had the best sensitivity. ERCP appeared to be the effective and preferred primary intervention of choice with failure rates being more in those having jaundice and dilated bile ducts. Delay in laparoscopic cholecystectomy following ERCP lead to a higher conversion rate to an open procedure. Serum alkaline phosphatase appeared to the best marker on follow up.

Keywords: common bile duct stone, common bile duct exploration, endoscopic retrograde cholangiopancreatography (ERCP).

Chapter 1

INTRODUCTION

Choledocholithiasis refers to the presence of stones in the common bile duct. It is a major health problem worldwide, particularly in the adult population. Autopsies of ancient Chinese and Egyptian mummies had revealed the existence of gallstones for at least 3500 years. The common bile duct stones are mostly secondary in origin and thought to have migrated from the primary site of origin in the gallbladder through the cystic duct. It is suspected in patients with symptomatic cholelithiasis, cholangitis and acute biliary pancreatitis. Primary choledocholithiasis is less common. Early identification of patients who are likely to have choledocholithiasis is essential since missed common bile duct stones can increase the risk of recurrent symptoms and life threatening complications like pancreatitis and ascending cholangitis.

Chapter 2

AIM

Evaluation of predictors for choledocholithiasis (common bile duct stones) and assessment of outcomes after treatment.

OBJECTIVES

1. To study the clinical, laboratory and radiological findings of patients diagnosed with common bile duct stones.

2. To study the current practice of managing this condition in our tertiary care hospital (Christian Medical College and Hospital).

3. To obtain data of a one year follow up of these patients who had undergone treatment for choledocholithiasis.

Chapter 3

REVIEW OF LITERATURE

3.1.0. Background

Gall stone disease is one of the most common and major health problem that requires hospital admission, particularly in the Western adult population (1). According to the National Health And Nutrition Examination Survey (NHANES III), over 20 million Americans are estimated to have gallstone disease (2). The prevalence of this disease shows ethnic variability and ranges from 10% to 15% in United States and Europe (3).

There is wide difference in prevalence of gall stones in India, with 2 to 4 fold higher prevalence in North Indians than the Southern population. Among the North Indians it was more prevalent in the Bengali community (4).

The clinical spectrum of this disease ranges from an asymptomatic state to fatal complications. Patients with asymptomatic disease have an annual risk of 1% for biliary colic (5), 0.3% for acute cholecystitis (6), 0.2% for symptomatic choledocholithiasis (7) and up to 1.5% for gall stone pancreatitis in 20 to 30 years (8),(9).

The patients presenting with symptomatic gall stones carry a risk of 5% to 12% for bile duct stones (10) and these are found in 18% to 33% of patients with acute biliary pancreatitis (11).

The primary bile duct stones are more prevalent in the Asian population. It can be either formed either intrahepatic or extrahepatic bile duct. These are usually brown pigment stone which are formed due to bacterial colonisation of bile and bile stasis (12),(13).

The secondary bile duct stones are due to the passage of gall bladder stones into the common bile duct. These are more common in the Western world and the elderly. They also occur frequently in those who had chronic inflammation of the common bile duct due to sclerosing cholangitis or parasitic infestation (14).

3.2.0. Overview of biliary anatomy

The anatomy of the biliary tree is variable and at times very complex, thus posing great challenges for diagnosis and treatment. A thorough knowledge of this complex anatomy and its variations is essential in radiologic, endoscopic, and surgical approaches to the biliary system.

3.2.1 Embryological development

The liver and the biliary system originate from the embryonic foregut. At four weeks a diverticulum arises from the ventral surface of the foregut. This liver diverticulum initially separates into a caudal and cranial portion, the caudal portion gives rise to the cystic duct and gallbladder and the cranial portion gives rise to the intrahepatic and hilar bile ducts. The ductal cells follow the development of the connective tissues around the portal vein branches. At first, the bile duct precursors are discontinuous but eventually they join one another and then connect with the extrahepatic bile ducts.

The extrahepatic biliary system is initially occluded with epithelial cells but later it canalizes as cells degenerate. The stalk that connects the hepatic and cystic ducts to the duodenum differentiates into the common bile duct (CBD).

Initially the duct is attached to the ventral aspect of the duodenum but when the duodenum undergoes rotation later on in development, there is repositioning of the CBD to the dorsal aspect of the duodenal wall (15).

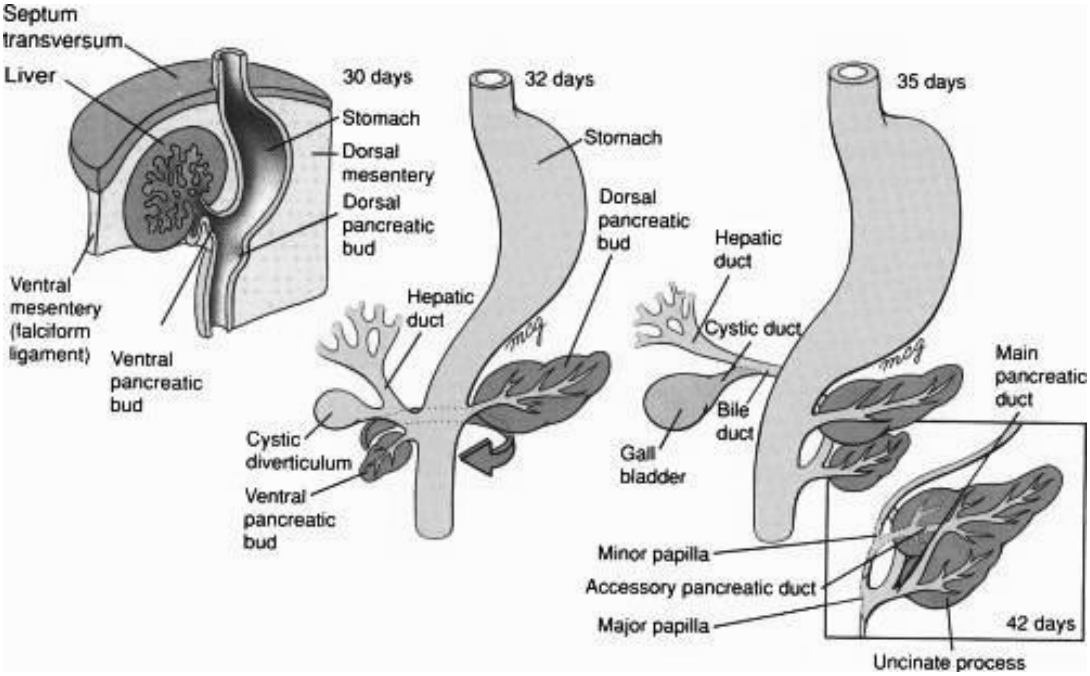


Fig.1 : The liver bud begins to expand into the ventral mesentery during the fourth week (16)

3.2.2 Intra hepatic anatomy

The hepatocytes secrete bile into the bile canaliculi. The bile flows through the canaliculi toward the center of the hepatic cords and drains into hepatic ductules which coalesce and drain into successively larger ducts in segmental pattern. The bile ducts draining each segment are considered third-order ducts. The sectoral bile ducts are second-order ducts with the main right and left ducts referred to as the first-order ducts (17). The hepatic ducts course along the portal vein and hepatic artery branches, which together constitute the portal triad.

3.2.3 Extra hepatic anatomy

The left and right hepatic ducts merge to form the common hepatic duct (CHD). The bile duct confluence is located in the hilar plate anterior to the portal vein. A sheath covers the bile duct and hepatic artery branches, which is continuous with the hepatoduodenal ligament in the extra hepatic region. There are many variations in the confluence pattern during the formation of the common hepatic duct.

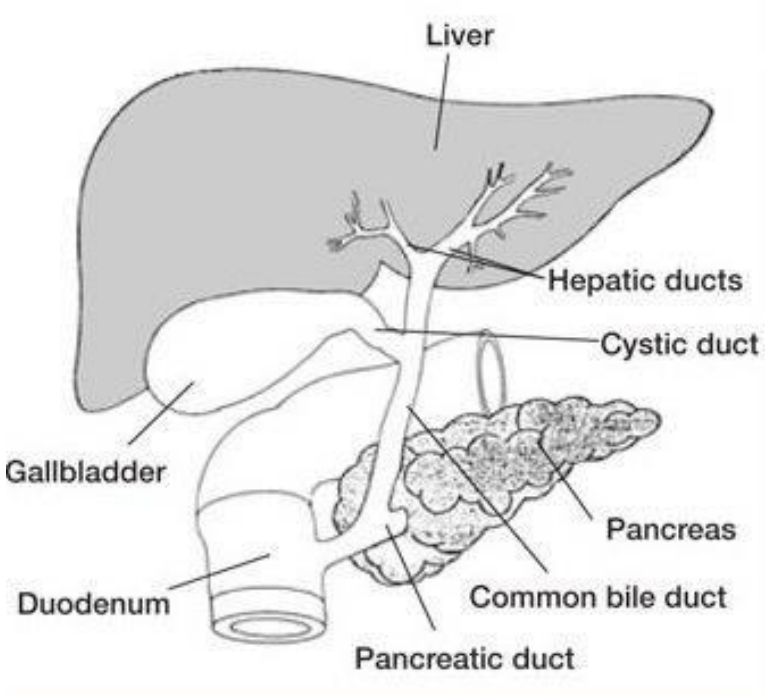


Fig.2 : Anatomy of liver, biliary system, duodenum and pancreas (18)

3.2.4. Common bile duct

The cystic duct from the gallbladder drains into the common hepatic duct to form the common bile duct (CBD). The CBD is situated anterior to the portal vein along the right edge of the lesser omentum. It courses caudad behind the first portion of the duodenum then runs in an oblique fashion on the dorsal aspect of the pancreas in the pancreatic groove.

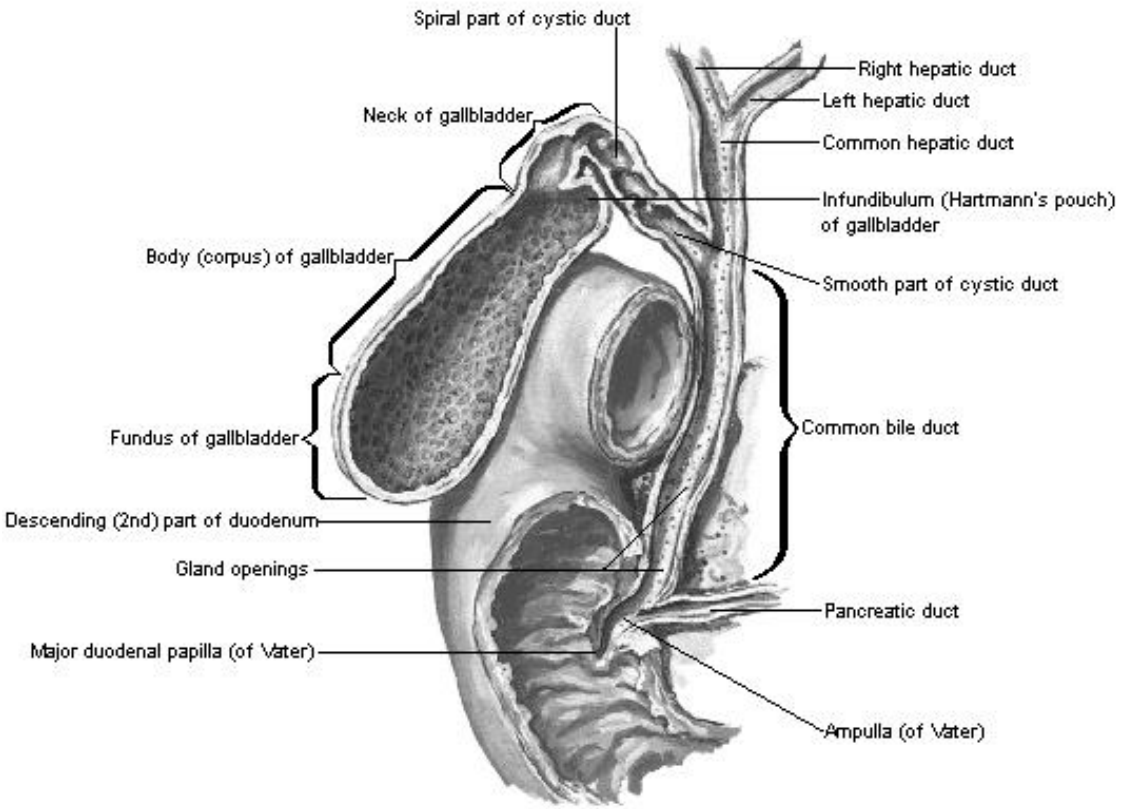


Fig.3 : Gallbladder and Extrahepatic bile ducts (19)

Most of the time, the CBD in the pancreatic groove is covered by pancreatic tissue or embedded within pancreatic tissue and in 12% of cases it has a posterior bare area (20). CBD usually joins the pancreatic duct (70%) and

they enter the second portion of the duodenum on its posteromedial wall at the major papilla (21).

The union of the CBD and the major pancreatic duct creates the ampulla of Vater. A sheath of circular smooth muscle fibres surrounds the ampulla and the intraduodenal portion of the CBD and the major pancreatic duct and is known as the sphincter of Oddi (22). In some cases, the pancreatic duct and the CBD do not join and each enters the duodenum separately on the duodenal papilla.

The site of entrance of the CBD into the duodenum has been studied by several groups and it was found that the CBD enters the descending portion of the duodenum in greater than 80% of the cases. Other sites of entrance of the CBD are the transverse duodenum and at the angle created by the junction between the descending and transverse duodenum (22).

Tab.1 : The varying diameter of CBD (20)

	External diameter (mean)	**Internal diameter (mean)**
Suprapancreatic CBD	5 – 13 mm (9 mm)	4 – 12 mm (8 mm)
CBD near duodenal papilla	constant	1.5 – 7.5 mm (4 mm)

There are several anatomic variations in which sectoral ducts may enter the CBD directly. These variations are uncommon but may be the cause for morbidity during biliary operation.

3.2.5. Blood supply

The extrahepatic bile ducts receive their arterial blood supply from several different major arteries. Northover and Terblanche (23) conducted a resin cast study in human cadavers in which they described two major axial vessels that ran along the lateral borders of the supraduodenal CBD. They named these the 3 o'clock and 9 o'clock arteries.

They reported an average of 8 small arteries with a diameter of 0.3 mm supplying the supraduodenal CBD. These arteries arise from below (posterior or anterior superior pancreaticoduodenal artery, gastroduodenal artery, retroportal artery) and above (right hepatic artery, cystic artery, left hepatic artery). In rare cases, there is nonaxial supply from the common hepatic artery (23).

The hilar ducts receive numerous arterial branches from the right and left hepatic arteries. These form a rich network around the ducts and are in continuity with the plexus around the CBD. In some cases, the 3 o'clock and 9 o'clock arteries may supply the hilar ducts. The retropancreatic portion of

the CBD is usually supplied by multiple small branches from the posterior superior pancreaticoduodenal artery.

Gunji and colleagues (24) used cadaver dissection and corrosion casts to describe a communicating arcade between the right and left hepatic arteries. They identified small branches from the communicating arcade that supplied the hilar bile ducts. At the time of biliary surgery, attention to the preservation of the blood supply to the bile ducts is imperative in the assurance of anastomotic integrity and the prevention of strictures.

A fine venous plexus that drains into marginal veins surrounds the surfaces of the extrahepatic and intrahepatic bile ducts (25). The marginal veins run in the 3 o'clock and 9 o'clock positions similar to the arterial vessels. Inferiorly, the marginal veins drain into the pancreaticoduodenal venous plexus. Superiorly, the marginal vessels have been shown to enter the hepatic substance or join the hilar venous plexus, which eventually drains into branches of the portal vein (26).The intrahepatic bile duct venous plexus drains into the adjacent portal vein. The veins of the gallbladder do not follow arterial branches and have direct drainage into the liver (27).

Due to the variability in anatomy and its complexity a preoperative assessment of the biliary and vascular anatomy by CT arteriography, venography, and cholangiography is of significant benefit during complex liver and biliary surgery.

3.3.0. Pathophysiology

The gallstones are classified into cholesterol stones and pigment stones according to the composition. Each type has a unique epidemiologic, structural, and risk factor profile. The framework contain poorly soluble component of bile that is precipitated on a three-dimensional matrix of mucin and proteins.

It is formed by cholesterol, calcium bilirubinates, and calcium salts of carbonate, phosphate or palmitate. The matrix is composed of large, polymeric mucin glycoproteins and small polypeptides (28).

Gallstones usually take many years to form and the estimated growth rate was found to be approximately 2mm per year (29) .

3.3.1. Cholesterol stones

These are the commonest stones that account for 80% to 90% of the gallstones in the developing world (30). They are usually composed purely of cholesterol or have cholesterol as their major constituent.

Cholesterol is usually soluble in the form of mixed micelles with an optimal concentration of bile salts and phospholipids. As bile becomes supersaturated due to disproportionate concentrations of the bile salts and fatty acid, the excess of cholesterol precipitates. These get embedded in the mucin gel with

bilirubinate to form biliary sludge. This eventually aggregates into a gallstone (31).

The chemical composition includes cholesterol monohydrate crystals, calcium salts, bile pigments, proteins and fatty acid. These are yellowish white in colour and can be as large as 4.5cms. Microscopically, they appear as thin, long crystals that are held together by a matrix of mucin glycoproteins. These gallstones are typically found in sterile environment.

3.3.2. Pigment stones

These stones contribute to about 20% of all gallstones and the percentage is much higher in Asian population. The excessive amount of unconjugated bilirubin becomes an important factor in the pathogenesis of pigment gallstone.

Bilirubin is the breakdown product of destroyed erythrocytes. It is conjugated in the liver with glucuronic acid producing diglucuronides (75% to 80%) and monoglucuronides (20%), which are secreted into bile as they are water soluble. About 3% of the bilirubin that reaches the liver is hydrolysed by β-glucuronidases and becomes unconjugated. These along with its calcium salts are poorly soluble in water. The levels in normal individual is not sufficient to promote stone formation, but in abnormal states the excessive amount of

unconjugated bilirubin becomes an important factor in the pathogenesis of pigment stones (28).

Black pigment stones contain predominantly calcium bilirubinate, but can also contain calcium carbonate and calcium phosphate in polymer-like complexes with mucin glycoproteins. They are formed in bacterially sterile environment. They are found in individuals with chronic haemolytic states like sickle cell disease and hereditary spherocytosis. They are also common in individuals with liver cirrhosis (32), Gilbert syndrome, cystic fibrosis and patients who have ideal disease like Cohn's disease (33) or post ideal resections.

Brown pigment stones are composed of calcium salts of unconjugated bilirubin along with varying amounts of cholesterol and protein. They are primarily in the bile duct as a result of bacterial infection that releases β-glucuronidases to hydrolyse glucuronic acid from bilirubin. The most common bacteria found are Escherichia coli, Bacteroides, and Clostridium. The stasis in the bile ducts and chronic anaerobic infection of bile promotes the accumulation of mucin and bacterial cytoskeletons in the bile ducts (34). Further ductal obstruction promotes more stasis and bacterial infection, thus perpetuating the cycle. Certain parasitic infections like Opisthorchis veverrini and Clonorchis sinensis lead to pigment stone formation, where the worm or egg directly stimulates stone formation. The calcified overcoat of the parasite

egg may serve as a nidus and enhance the precipitation of calcium bilirubinate (35).

Tab.2 : Characteristics of gallstones (36)

	Cholesterol	**Brown-pigment stone**	**Black-pigment stone**
Origin	Gallbladder (secondary stones)	Ducts ± gallbladder (primary stones)	Gallbladder ± ducts (primary stones)
Component	40–70% cholesterol	15% cholesterol 60% calcium bilirubinate 15% calcium phosphate	2% cholesterol 6% calcium carbonate 40% calcium bilirubinate 9% calcium phosphate
Predisposing factors	- Obesity - Bile duct pool -↑Cholesterol synthesis -↑Progesterone	- Diet: low protein, high carbohydrate - Cholangitis - Biliary stricture - Biliary infection: Bacterial or parasitic - Biliary stasis: total parenteral nutrition, vagotomy	- Cirrhosis - Chronic hemolysis - Sickle cell anaemia - Heart valve replacement

	Cholesterol	Brown-pigment stone	Black-pigment stone
Shape, size, number	Multiple: smooth faceted Single: smooth, round ≥2.5cms	Smooth, round 1-3cms	Multiple, irregular or smooth <0.5cms
Physical characteristics	Hard, laminated	Hard	Soft, friable

3.4.0. Risk factors

The risk factors for gallstones can be broadly divided into modifiable and non-modifiable. The environmental factors and genetic predisposition play an interactive role in the formation of gall stones. The inflammatory immune response by the individual also plays a role in the susceptibility to stone formation (37).

The role of genes in the formation of gall stones is more evident as there is a difference in prevalence with geographic and ethnic variations. There is increase in incidence of gallstones in families and identical twins of patient with gallstones (3).

Tab.3 : Factors attributing to the formation of gallstones (38)

Modifiable factors	Non-modifiable factors
Pregnancy and parity	Increasing age
Obesity	Female gender
Low-fibre, high-calorie diet	Ethnicity
Prolonged fasting	Genetics, family history
Drugs: clofibrate, ceftriaxone	
Oral contraceptives	
Low-level physical activities	
Rapid weight loss (> 1.5 kg/week)	
Hypertriglyceridemia or	
low high-density lipoprotein	
Metabolic syndrome	
Gallbladder stasis	
Specific diseases (i.e. Cirrhosis,	
Crohn's disease with severe ileal involvement or resection)	

The genes involved in the transport of biliary lipid and lipid metabolism have also been identified (39). Individuals with impaired gallbladder contractility are also prone for denovo stones and also recurrent gallstones post therapy.

3.5.0. Prevention

There are few steps which can lower the risk of gallstone formation which include moderate physical activity and dietary modification with high fibre intake and avoidance of saturated fatty acids (40).

Prevention of gallbladder sludge in patients receiving prolonged total parenteral nutrition was prevented by daily administration of cholecystokinin (41). Patients receiving long term somatostatin therapy or having rapid weight loss have benefited from oral ursodeoxycholic acid (UDCA), one of the secondary bile acids which are metabolic by-products of intestinal bacteria, in prevention of gallstones. There is currently insufficient data to support UDCA for its use to prevent biliary colic or prevention of complications in patients with gallstones awaiting cholecystectomy or unfit for operation (42).

3.6.0. Clinical spectrum

As described earlier the common bile duct stones can be primary bile duct stones that originate in the bile duct or secondary bile duct stones that have descended from the gallbladder (43). The dominant component in primary stone is bilirubin and in secondary stone is cholesterol, so it is important to distinguish between them. The primary stone often requires a more complex

drainage procedure to prevent recurrence as compared to secondary stones (44).

Patients with common bile duct stones (CBDS) have varied signs and symptoms, being asymptomatic to having biliary colic, jaundice, cholangitis or pancreatitis (45). The prevalence of asymptomatic CBDS is between 5.2% to 12% (10). A most common presentation of common bile duct stones is biliary colic. This is described as pain, often situated in the right hypochondrium or epigastrium which can last from 30 minutes to several hours, with associated symptoms such as nausea and vomiting (45). Other presentations include jaundice, caused by increased levels of bilirubin in the blood which manifests as yellowish pigmentation of the skin, the conjunctival membranes over the sclerae (whites of the eyes), and other mucous membranes. Pale stools and dark-coloured urine are the other symptoms associated with it (46).

Other two serious, life-threatening complications of common bile duct stone include cholangitis and gallstone pancreatitis. The acute obstructive ascending cholangitis is caused by infection of the obstructed biliary ductal system. The commonest organism cultured is E.coli and it responds with antibiotics in more than 75% of cases (47). The classical symptoms of Charcot's triad which includes right upper quadrant pain, jaundice and fever may be encountered. Less common is Reynolds's pentad which includes

shock and altered mental status (44). Despite the advancement in therapy, acute ascending cholangitis carries a mortality rate of 10% to 20% (48).

It is difficult to infer why some patients with gallstones suffer from pancreatitis while others are spared of this potentially lethal complication. A study using insitu cholangiogram catheter showed spontaneous passage of bile duct stone in approximately one third of patients, based on stone disappearance six weeks after diagnosis (49). Recent studies show that there was increased risk of pancreatitis with small gallstones, excess cholesterol crystals, and good gallbladder emptying (50),(51). Small gall stones caused more distal obstruction that lead to bile reflux into the pancreatic ducts which in turn activated release of pancreatic enzymes into the glandular interstitium with duct injury (52). Though majority are self-limiting disease, the mortality can go upto 10% (53). The mortality rate remains less than 1% for mild acute pancreatitis and can go upto 10% to 30% for severe acute pancreatitis (54).

Patients with symptomatic bile duct stones if left untreated are at high risk of recurrent symptoms and complications. During a follow up period of six months to 13 years, a study showed recurrent symptoms in more than one half of patients who had retained bile duct stones (55) and 25% of patients developed serious complications (45). Therefore specific therapy is indicated regardless of the symptoms due to the potential serious complications of bile duct stones.

3.7.0. Diagnosis

In the recent era of widely available advanced technology, a clinical approach still remains paramount. A clinician should be able to recognise the typical as well as atypical presentations. The newer techniques of biliary imaging have simplified the diagnosis of bile duct stones, with non-invasive methods having lower risk and invasive techniques having greater accuracy.

3.7.1. Laboratory Tests

Patients with the above clinical spectrum require further diagnostic laboratory investigations to assess for the presence of common bile duct stone. **The liver function tests (LFT's)** is used as a screening blood investigation for CBDS (56). An *elevated serum bilirubin and alkaline phosphatase* are considered as markers of biliary obstruction. But these are neither highly sensitive nor specific (57). Elevated alkaline phosphatase and serum gamma glutamyl transpeptidase (GGT) were the most frequent abnormalities (upto 90%), noted in the laboratory valves by Anciaux et al in patients with symptomatic CBDS (58). Elevated serum bilirubin levels is more common during complete obstruction of the bile duct (45). There have been case studies by Murohisa et al. (59) and Sheen-Chen et al. (60) which reported high level CA 19-9 in CBDS with cholangitis. There are rare reports which shows profound elevation in serum transaminase levels (up to 2000 IU/L), mimicking viral

hepatitis, but decline rapidly over several days unlike viral syndromes which take a longer duration(61). Laboratory studies therefore must be used in addition to imaging modalities to predict the presence of CBDS.

3.7.2. Imaging Modalities

Trans abdominal ultrasonography (TUS) is the first line of investigation in patient suspected with common bile duct stone (45). The sensitivity and specificity for detecting CBDS is between 25% to 63% and 95% respectively (62). But the dilation of the common bile duct and the investigators' experience plays an important role. Barkun et al. predicted CBDS upto 95% in patients older than 55 years with abnormal liver enzymes and CBD dilation on ultrasonography (63).

Endoscopic retrograde cholangiopancreatography (ERCP) was considered as the gold standard test for the detection of CBDS (45). Earlier this was used primarily in diagnosis, but today it's reserved as a therapeutic modality (46). ERCP has sensitivity of 90% to 95% (64),(65) and a specificity of 92% to 98% in detecting CBDS (66),(67). Christensen et al showed that this procedure was associated with a morbidity and mortality rate of 15.9% and 1% respectively (68).

Endoscopic Ultrasound (EUS) involves insertion of an endoscopic ultrasound probe through the stomach and up to the second half of the duodenum for imaging CBD. This would have the advantage of not having the interference from the subcutaneous fat or that from bowel gas (69). The sensitivity is about 95%, and the specificity was between 95% to 98% (70). This was more sensitive than trans abdominal ultrasound and its sensitivity is compared to that of diagnostic ERCP. This procedure had less morbidity as compared to ERCP, which was a major advantage (46). EUS is a relatively non-invasive test with excellent sensitivity and specificity for diagnosing CBD stones, but it is highly examiner dependent.

Magnetic Resonance Cholangiopancreatography (MRCP) has emerged as an accurate, non-invasive diagnostic modality for evaluating the biliary ducts (71). It was helpful in identifying patients who would benefit from early intervention (72),(73). A recent meta-analysis showed that MRCP had an excellent overall sensitivity of 95% and a specificity of 97% in diagnosing the level and presence of biliary obstruction (74). EUS and MRCP had similar detection rate of CBDS (75). The major disadvantages of MRCP were unit availability, the lower spatial resolution (76), potential claustrophobia, and the inability to evaluate patients with ferromagnetic implants or pacemakers (77).

Intraoperative Cholangiography (IOC) is the technique where the cystic duct is catheterised and radio-opaque dye is injected to study the biliary anatomy. The routine use of IOC is still controversial, there are groups favouring and others advocating only a selective use and while others report no advantage with respect to missed CBDS (78),(79),(80). However it is found to be an useful tool to identify CBDS (57). This is performed during laparoscopic or open cholecystectomy. The sensitivity of IOC was 98% and specificity was 94% in detection of common bile duct stones (81). The various causes for failure of IOC include inability to cannulate the cystic duct, air bubbles mimicking stones, leakage of contrast fluid during the injection , spasm of the sphincter of Oddi and failure to fill the biliary tree because of too rapid contrast flow. Supporters of this procedure claim that this ensures fewer retained stones, reduction in common bile duct injuries and postoperative ERCPs (82),(83). This procedure adds about 15 minutes to the overall operating time (84).

Conventional Computed Tomography (CT) is the other modality available with a sensitivity of 87% and a specificity of 97% for the diagnosis of CBDS (85),(86). Kondo et al. found that CT scanning was equivalent to MRCP, but had the risk of allergic reaction to contrast used (87).

Intraductal Ultrasonography (IDUS) has been useful in identifying residual small stones after endoscopic lithotripsy or when ERCP is not diagnostic. Though IDUS is found to increase the sensitivity and specificity in the diagnosis of CBDS, there is notable increase in procedure time of about 7 to 15 minutes (88).

Percutaneous Transhepatic Cholangiography (PTC) is the modality of choice in patients with previous gastric operation, distal impacted stones, failed ERCP, intrahepatic stones or in patients with cholangiohepatitis.

Choledochoscopy are miniature endoscopes that can be introduced into the bile duct through the duodenoscope during ERCP or IOC. These help in nonsurgical management of difficult biliary stones. The direct visualization of the biliary epithelium provides additional data in the assessment of biliary strictures, targeted tissue acquisition, targeted therapy, and wire guidance (89). Therefore Choledochoscopy has a dual purpose in diagnosis as well as therapy. Intraoperative cholangiography had better outcomes regarding stone clearance when it is assisted by Choledochoscopy. Both open and laparoscopic Choledochoscopy had no difference in stone clearance rate.

Tab.4 : Characteristics of the imaging studies for diagnosis of common bile duct stones (38)

Characteristics	TUS	CT	MRCP	EUS	ERCP
Sensitivity (%)	25-63	71-75	85	93-98	90-97
Specificity (%)	95-100	97	93	97-100	95-100
Advantages	Inexpensive, Safe, Widely available, Portable	Detection of concomitant intrahepatic duct stones, liver parenchymal lesions, and pancreatic lesions	High accuracy for duct stone detection, Non-invasive intrahepatic and extrahepatic duct evaluation	High accuracy for duct stone detection, Less invasive than ERCP, Detects small stones in a non-dilated duct	High accuracy, Therapeutic potential

Characteristics	TUS	CT	MRCP	EUS	ERCP
Disadvantages	Low sensitivity, Operator dependent	Radiation exposure, Contrast allergy, Renal impairment	Expensive, Time consuming, Limited value in stones < 6 mm, impacted stone at the ampulla and dilated bile duct >10 mm, Claustrophobia Ferromagnetic implant, Artefact interference	Operator dependent, High cost of equipment, Insensitive for proximal common hepatic duct / intrahepatic duct stones	Higher risk than EUS, False positives (air bubbles), False negatives with small stones in dilated duct, Unsuccessful cannulation

3.8.0. Treatment

Patients with CBDS often times present with complications like cholangitis or gallstone pancreatitis are acutely ill. They will require aggressive hydration and antibiotic therapy (46). E.coli and Klebsiella species are the commonly detected gram negative bacteria in the bile culture. In recent decades there has been polymicrobial cultures due to wide spread use of antibiotics and increased instrumentation (52). Patient characteristics and regional antibiotic sensitivity patterns govern the choice of antibiotics. The first line of treatment is a combination of an aminoglycoside with amoxicillin-clavulanic acid (52). If there are contraindications for aminoglycosides, then broad spectrum penicillin is a reasonable alternative.

The therapeutic management of CBDS is based on the local availability of expertise. The two broad management of CBDS are pre or postoperative ERCP with endoscopic biliary sphincterotomy (EST) proceed later with cholecystectomy and the other is a single stage procedure of surgical bile duct clearance and cholecystectomy. Many studies had revealed the similar effectiveness of both methods of treatment (90),(91). Kharbutli et al. showed one-stage management had less morbidity and mortality (7% and 0.19%) than a two-stage management (13.5% and 0.5%) (92).

There are other modalities of treatment such as electrohydraulic lithotripsy (EHL), extracorporeal shockwave lithotripsy (ESWL), laser lithotripsy and dissolving solutions which are indicated only in special situations.

3.8.1. Preoperative Endoscopic Management

In recent decades, ERCP/EST had gained more acceptance in clearing CBDS. The success rate of an isolated ERCP treatment was up to 87% to 97% and two or more ERCP treatment was needed in 25% of the patients (93). The morbidity associated with this procedure was 5% to 11% and mortality rates of 0.7% to 1.2% (94),(95). The various complications included bleeding, duodenal perforation, cholangitis, pancreatitis, and bile duct injury (96). A follow up study showed symptom free period of up to 70 months (97). ERCP was not possible in 3% to 10% of all patients (98). ERCP/EST was preferred in patients with CBDS presenting with cholangitis, pancreatitis and increased age with substantial comorbidity.

Endoscopic balloon dilation of the papilla is an alternative method to sphincteroplasty as it is easier (99) with lower bleeding rate (100) and better preservation of the of function to the sphincter of Oddi (101). But many randomised trials showed endoscopic balloon dilation had more failure rate and higher rate of pancreatitis in comparison EST. Therefore EST is preferred in stone extraction unless contraindicated due to coagulopathy (102).

For patients with retained stone it is important to ensure adequate biliary drainage, therefore short term use of biliary stent followed by further endoscopy or surgical treatment is advocated (102). Stenting is also considered as an alternative in patients over 70 years of age or with debilitating disease (103). It is a "bridge" until further definitive treatment for CBDS is executed.

When laparoscopic common bile duct exploration fails or if there are retained stones after the operation (2.5%), ERCP is used as a treatment modality (104). In selected patients transhepatic therapies can be considered for CBDS (57).Those with previous gastric bypass operations where majority of the stomach, duodenum and proximal jejunum are bypassed, endoscopic access via a gastrostomy or jejunostomy have been described (105).

3.8.2. Laparoscopic Common Bile Duct Exploration (LCBDE)

Laparoscopic biliary surgery has become safe and cost effective with advancing technology. The successful outcome depends on several factors including surgical expertise, the biliary anatomy, the number and size of CBD stones and adequate equipment (106). LCBDE has successful stone clearance rates ranging from 85% to 95% and associated morbidity of 4% to16% and a mortality of 0% to 2% (107). Tai et al. reported 100% clearance rate with no recurrence during a follow up period of 16 months with LCBDE (96). Therefore it is used in clearing difficult stones and also to manage acute

gallstone cholangitis (108). The complications of this procedure include CBD laceration, bile leak and stricture formation (109). They also had a shorter hospital stay and lower hospital costs (110).

There are two approaches to LCBDE either via the cystic duct or trans-ductal. If CBDS are detected at the time of laparoscopic cholecystectomy by IDUS, IOC, or other modalities, the best treatment for an undilated bile duct is a trans cystic approach for stone clearance. On failing alternate approaches such as intraoperative or postoperative ERCP/EST may be done. While for a dilated common bile duct this may be treated at the same time by a laparoscopic choledochotomy, or open CBDE (111).

LCBDE Trans-Cystic Approach

This approach is generally used for small stones in a undilated bile duct (98). In this approach 100 to 200mL isotonic sodium chloride solution with 1 to 2 mg glucagon (for relaxation of Oddi's sphincter) is used to irrigate and flush the stones.

If unsuccessful, a helical basket can be used under fluoroscopic guidance over a guide wire. If this fails, a choledochoscope (≤10 French) should be used to remove the stones under direct vision (112). Balloon dilation of the cystic duct can be attempted for larger stone, but never dilated larger than the internal diameter of CBD (113). Isotonic sodium chloride solution irrigation

of CBD is done for better visualization. A cholangiogram or ultrasound is done to confirm clearance (112).

This approach proved to be consistent with the goals of a laparoscopic approach with minimal morbidity without a T-tube or a drain and a rapid recovery in most cases (114).

Other novel procedures described are the trans cystic balloon dilatation of the sphincter of Oddi and ante grade sphincterotomy. This is done when other measures fail to clear the stone. There is risk of developing pancreatitis with this method. It is safe to avoid this technique in patients with pre-existing pancreatitis, CBD dyskinesia, or sphincter anomalies.

Recent series show successful trans cystic duct clearance has been described in 80% to 98% of patients (107). Infection and pancreatitis have been reported in 5% to10% of patients and the mortality rate was 0% to 2%. The average hospital stay post procedure was approximately 1–2 days. The main advantage is that it avoids choledochotomy (112).

LCBDE Trans-Ductal Approach

This approach is preferred for large occluding stones in a large duct, intrahepatic stones, or an extremely small or tortuous cystic duct. The various approaches include dilation of the distal CBD, balloon catheter or basket or choledochoscopic manipulation with or without fluoroscopic guidance (115)

as well as IOC. After the stone extraction the ductotomy is usually closed either primarily or over an appropriately sized T-tube.

The T-tube helps in decompression of the duct, ductal imaging in the postoperative period and providing an access route for the removal of residual CBD stones (114). Usually a longitudinal choledochotomy of over a distance of approximately 1 to1.5 cm is preferred. A 14-French latex T-tube or larger is closed over using 4-0 monofilament absorbable sutures. Trans cystic tubes (C-tube) or ante grade stenting with choledochorrhaphy for CBD drainage (116) has also been described.

The complications of T-tubes in the postoperative period involve bacteraemia, dislodgment, obstruction or fracture of the tube (117). The patient is generally discharged 2 to 4 days post procedure. T-tube cholangiography is done prior to the removal of the tube by 10 to14 days postoperatively. Removal can be delayed as late as 4 to 5 weeks after surgery. Retained stones can be removed through the matured tract and is 95% successful. If unsuccessful post-operative ERCP may be attempted (112).

Due to potential complications of T-tube drainage, primary closure of the CBD without drainage has been advocated by some authors in open biliary tract surgery (118). Studies showed shorter operating time, greater patient satisfaction, reduced hospital stay (18.3 days versus 31.5 days) (119), reduced expenses, early return to work (12.6 ± 5.1 versus 20.4 ± 13.2 days),

reduced postoperative complications (15% versus 27.5%) and biliary complications like bile leakage or biliary peritonitis (10% versus 20%) in primary closure as compared to T-tube drainage (120). It was noted that laparoscopic trans cystic CBDE is less invasive and was associated with lower complication rate, but higher failure rates when compared to trans ductal approach (121).

3.8.3. Open Common Bile Duct Exploration

Many randomized controlled show superior outcomes for standard open bile duct surgery as compared to the endoscopic treatment of CBDS(110). This is used when the laparoscopic and endoscopic methods have failed. Martin et al. reported greater success and lower mortality with open surgery than ERCP in CBDS (91).

Choledochoenterostomy or a sphincteroplasty are two options along with open common bile duct exploration. The experience of the surgeon usually dictates the approach.

Choledocoenterostomy is done in the setting of dilated CBD (size greater than 2cms) with multiple stones or recurrence with distal obstruction (112). This provides drainage with good long-term results. The commonly performed technique is a side-to-side choledochoduodenostomy where supraduodenal CBD is anastomosed to the duodenum (122). Kocher

manoeuvre is performed to expose the distal CBD, and choledochotomy is made within 2-3 cm of the lateral border of the duodenum. A hand sewn diamond-shaped anastomosis is performed with interrupted absorbable sutures.

“Sump syndrome” is a potential rare complication (1%) caused by food or other debris caught in the distal CBD (123), usually managed with ERCP/EST (124).

Sphincteroplasty consists of incising the distal part of the sphincter musculature and suturing the ductal mucosa to duodenal mucosa. Sphincteroplasty is performed following choledochotomy. A catheter or dilator is passed distally after mobilising the duodenum by Kocher manoeuvre. Then a duodenotomy is performed at the level of the ampulla. Then ampulla is incised sufficiently along the anterosuperior border opposite the pancreatic duct opening to remove the impacted calculus (112).

Other alternative operations include transection choledochoduodenostomy where the distal trans pancreatic segment of the bile duct is excluded and an end to- side anastomosis of the transected common bile duct with the second part of the duodenum is performed. This procedure has an excellent long term results (122). Another commonly performed technique is the choledochojejunostomy with a roux-en-Y loop.

3.8.4. Electrohydraulic Lithotripsy (EHL)

This technique uses shockwave generated by high voltage to fragment the bile duct stones. This is done under cholangioscopic or fluoroscopic guidance using a balloon catheter (123). It is indicated in packed multiple stones or an impacted single large stone. There is increased risk of damaging the bile duct wall if the stone is not targeted under direct sight (124). There is high risk of tissue damage and bleeding.

3.8.5. Extracorporeal Shockwave Lithotripsy (ESWL)

This technique was first used 1980s following its successful use in fragmenting renal calculi (45). This involves percutaneous administration of sound waves directed at the liver and bile duct. This is used prior to ERCP to fragment large stones and facilitate its removal. Few European studies show duct clearance rates of 83% to 90% (125).

3.8.6. Laser Lithotripsy

This technique uses amplified light energy at a particular wavelength focussed into a single beam (45). This can be performed under direct vision or fluoroscopic guidance. Several studies show a success between 64% to 97% for clearing retained stones (126).

3.8.7. Dissolving Solutions

Several types of solutions are available for dissolving gallstones and CBDS which have few toxic side effects and no irritation to the biliary tree. Ideal solvent is yet to be discovered.

Ursodeoxycholic acid (UDCA) and chenodeoxycholic acid has been shown to dissolve cholesterol-containing stones. This is beneficial to the western population where the majority of the stones are cholesterol stones. UDCA therapy showed prevention of recurrence of gallbladder microlithiasis (127).

Methyl-Tertbutyl-Ether (MTBE) is excellent cholesterol solvent but it is toxic to duodenal mucosa and liver.

3.9.0. Recurrent common bile duct stones

Recurrence of CBD stones after endoscopic stone removal is 4% to 24% (128), either from de novo primary stone formation or secondary migration from the gallbladder (129). Primary CBDSs are associated with bactobilia and delayed bile-duct clearance. Dilated main duct (≥13 mm) and the presence of a periampullary diverticulum are common risk factors for recurrent stones.

Endoscopic re-intervention is performed and surgery is reserved for intractable cases. Patients prone for stone formation (low-phospholipid associated cholelithiasis) should be identified and preventive medical treatment with UDCA can be considered (129). The correctable risk factors such as biliary strictures, papillary stenosis, and gallstones in patients who have gallbladder in situ should be identified and treated to prevent recurrence.

Chapter 4

METHODOLOGY

Cohort of patients diagnosed with choledocholithiasis who presented to the outpatient clinic of Hepatic Pancreatic and Biliary Surgery, General Surgery and Gastroenterology departments at Christian Medical College, Vellore from July 2008 to June 2012 were included in the study following acceptance by the Institutional Review Board. Follow up data was noted for these patients from the available clinical record. This retrospective descriptive study will obtain information from the records based on a standard performa. The details will include clinical symptoms, physical findings, biochemical tests and radiological reports. In addition the immediate outcome of the different modalities of management, and a one year follow up report of the patients will be noted from chart reviews. The inpatient and outpatient medical records of each patient were collected by the same person to avoid interpersonal variability.

4.1.0. Inclusion criteria

1. Patients with diagnosis of choledocholithiasis between July 2008 and June 2012

2. Patients with a first time diagnosis of choledocholithiasis

3. Age above 18 years

4. Treatment naive patients with respect to present attack of choledocholithiasis

4.2.0. Exclusion criteria

1. Other biliary tract diseases

2. Liver parenchymal disease

3. Previous biliary tract operations or procedures (except previous cholecystectomy, laparoscopic or open)

4. Suspected carcinoma gallbladder

4.3.0. Confounders

Patients from lower socioeconomic strata may not be able to afford the more expensive diagnostic tests, so this may account for missing data.

Other factors like assessment of clinical profile by different doctors, non-availability of all data involved in the investigations and treatment, and associated co-morbidities could have led to the change in treatment modality.

4.4.0. Bias

1. Information bias:

   From the chart reviews there were missing data.

2. Observer bias

   Inter-doctor variability in clinical examination.

3. Treatment bias

   Variability in management between the surgical and medical department.

4.5.0. Statistical methods

The various statistical methods used in this study were;

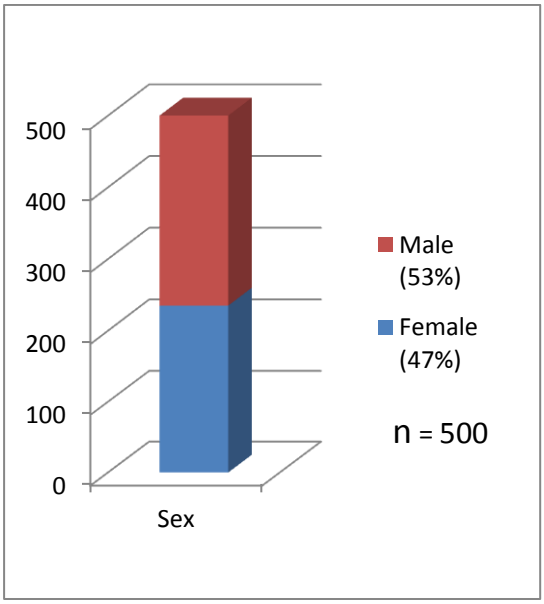
1. Descriptive statistics was done with Mean +/- 2 SD.
2. Categorical variables were analysed using Chi-square test.
3. Continuous variables were assessed using two independent variable ‘t’ test after checking for normality.
4. Non normal data was analysed using Mann Whitney U test.
5. Multivariant analysis was done to predict the pre-operative diagnosis using binary logistic regression for biochemical variable.
6. Two proportion test was used to correlate association.

Chapter 5

RESULTS

A total number of 500 patients with choledocholithiasis, had presented to CMCH, Vellore during the study period July 2008 to June 2012. The demographic data of the study group;

Fig.4: Sex ratio



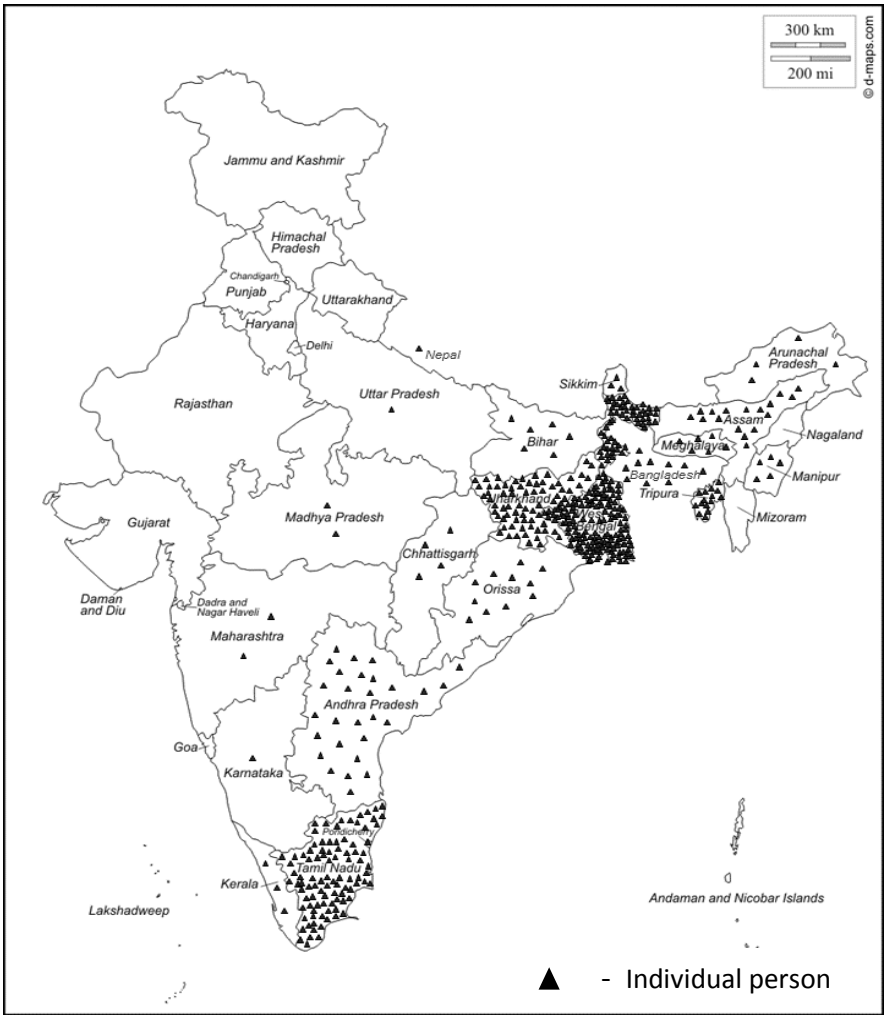
The demographic data showed a male population of 53% and a female population of 47%.

Tab.5: Distribution of the data studied

Study	Number	Minimum	Maximum	Mean	Std. Deviation
Age	500	18	89	52.14	14.161
BMI	47	16.7	31.1	22.151	3.6717
S. Bilirubin	489	0.2	40.3	3.193	5.1042
SGOT	490	11	1126	77.52	99.574
SGPT	490	5	795	75.01	91.292
S. Alkaline phosphate	490	37	3281	258.52	260.162
LDH	57	230	2220	658.54	409.603
S.Amylase	191	6	19000	768.29	1967.272
S.Lipase	179	5	33490	1658.59	4558.618
Total Cholesterol	161	77	511	181.77	56.161
Triglyceride	162	24	551	168.30	97.289
S.LDL	162	7	791	109.87	67.074
Haemoglobin	476	5.1	16.9	11.844	1.9097
AC	221	53	469	120.19	58.111
PC	231	70	864	162.84	102.939
INR	446	0.1	3.9	1.063	0.2560
CBD size	269	3.7	37.0	11.558	4.7625

The data distribution showed an age distribution ranging from 18 to 89 years with a mean age of 52 years.

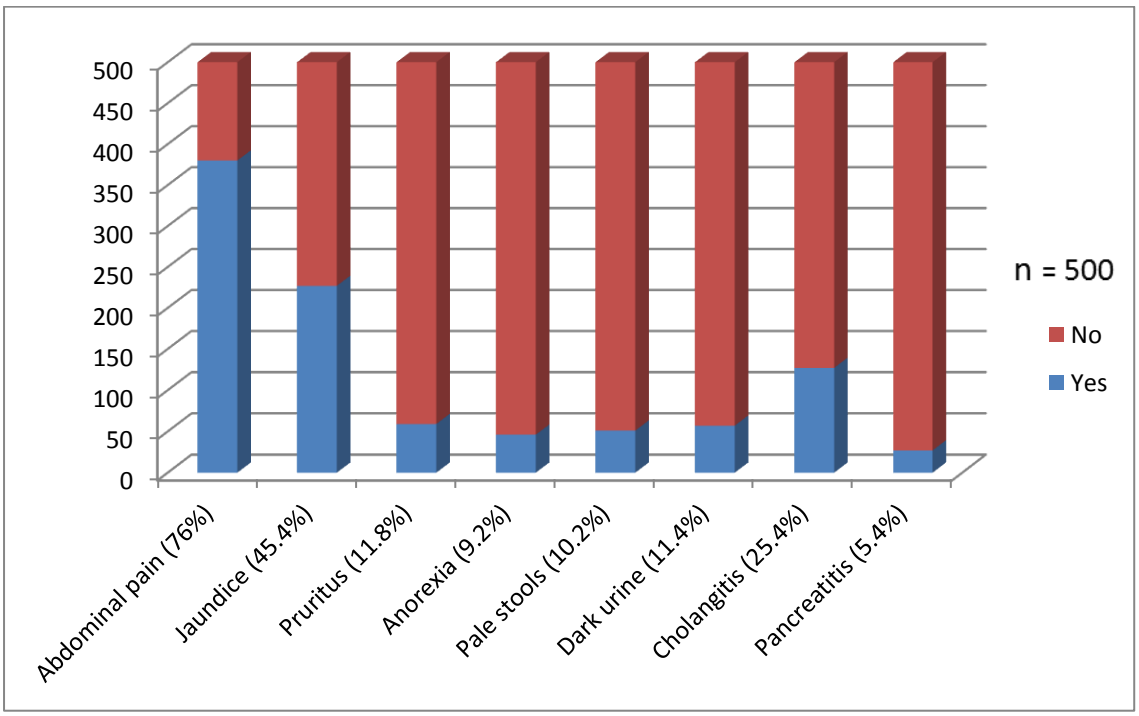
Fig.5: Population distribution of the study group



States	Frequency	Percent	States	Frequency	Percent
Andhra Pradesh	28	5.6	Manipur	5	1.0
Arunachal Pradesh	4	0.8	Meghalaya	6	1.2
Assam	17	3.4	Nepal	1	0.2
Bangladesh	10	2.0	Orissa	11	2.2
Bihar	6	1.2	Pondicherry	1	0.2
Chhattisgarh	4	0.8	Sikkim	3	0.6
Jharkhand	70	14.0	Tamil Nadu	95	19.0
Karnataka	1	0.2	Tripura	15	3.0
Kerala	3	0.6	Uttar Pradesh	1	0.2
Madhya Pradesh	2	0.4	West Bengal	215	43.0
Maharashtra	2	0.4	Total	500	100.0

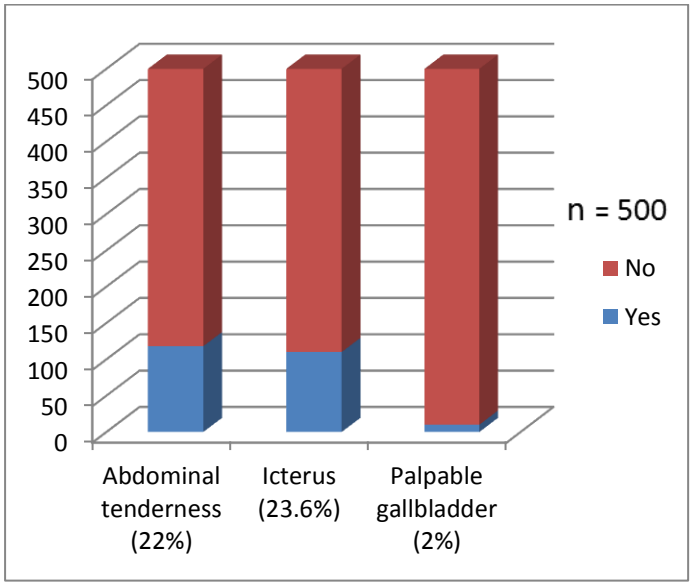
The majority of the population were distributed over the eastern states. The states of West Bengal (43%) followed by Tamil Nadu (19%) and Jharkhand (14%) constituted the majority of the study population.

Fig.6: The frequency of clinical symptoms during presentation



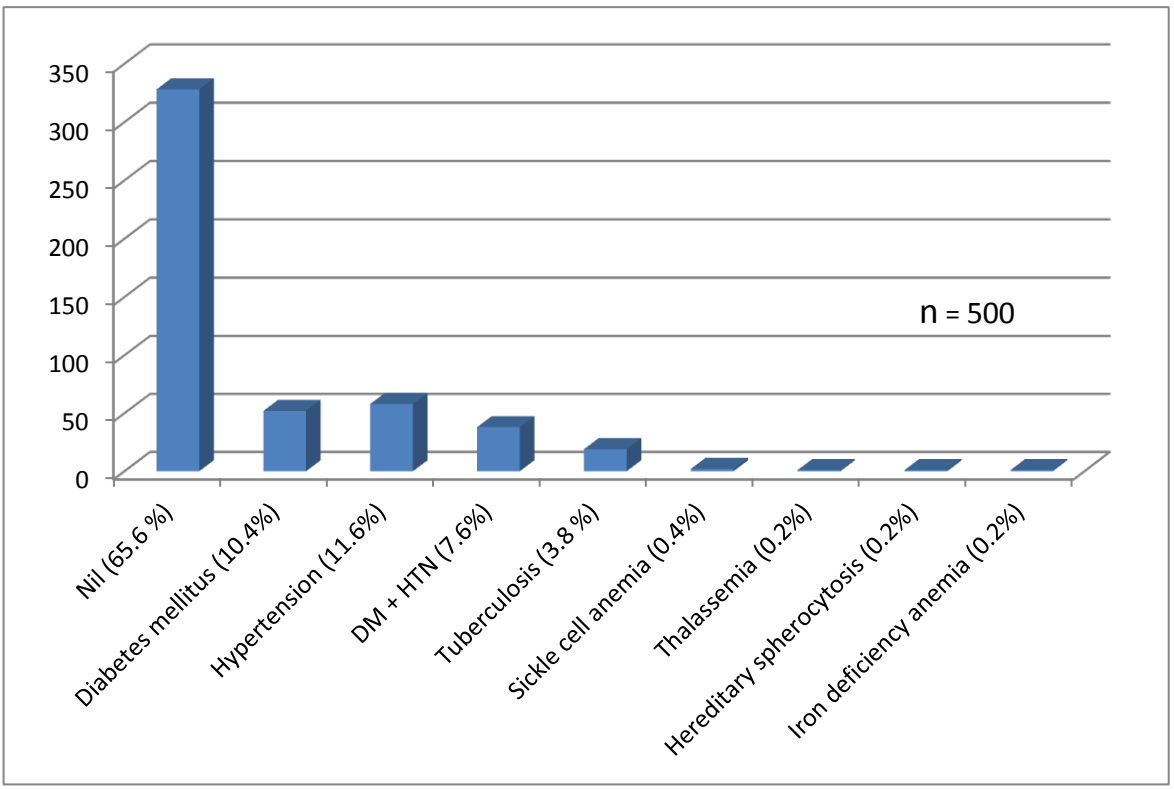
The above graph showed the predominant clinical symptoms at presentation were abdominal pain (76%), followed by jaundice (45.4%), and cholangitis (25.4%).

Fig.7: The frequency of clinical signs during presentation



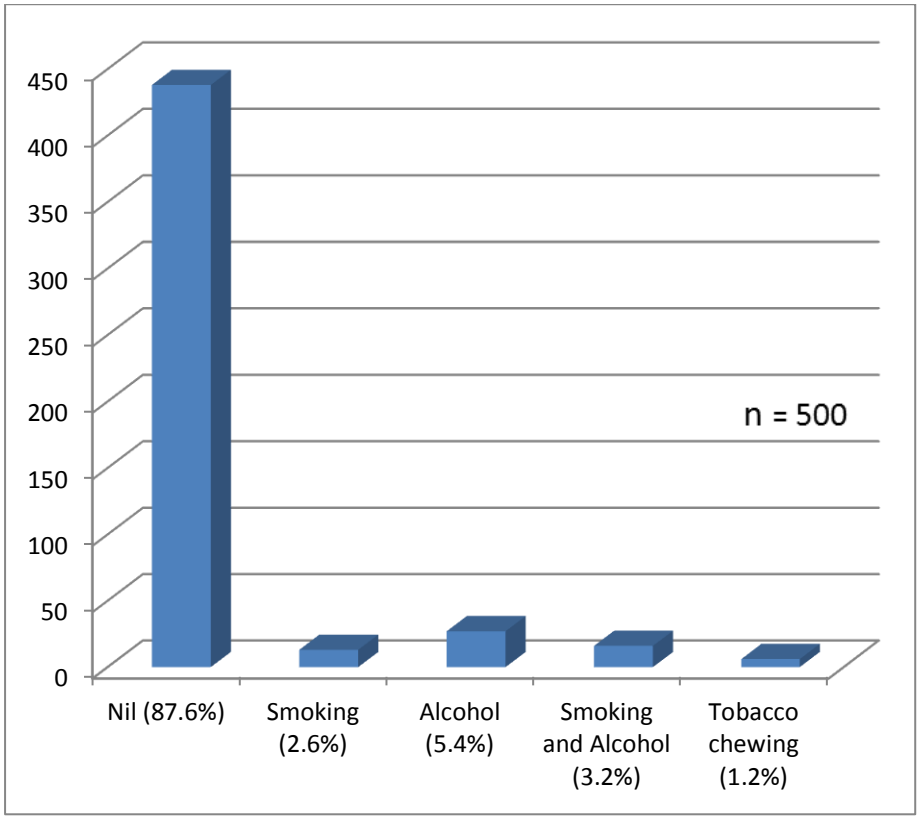
The above graph showed that majority of the patients did not have any major clinical signs at presentation.

Fig.8: The co-morbidities associated with the patients



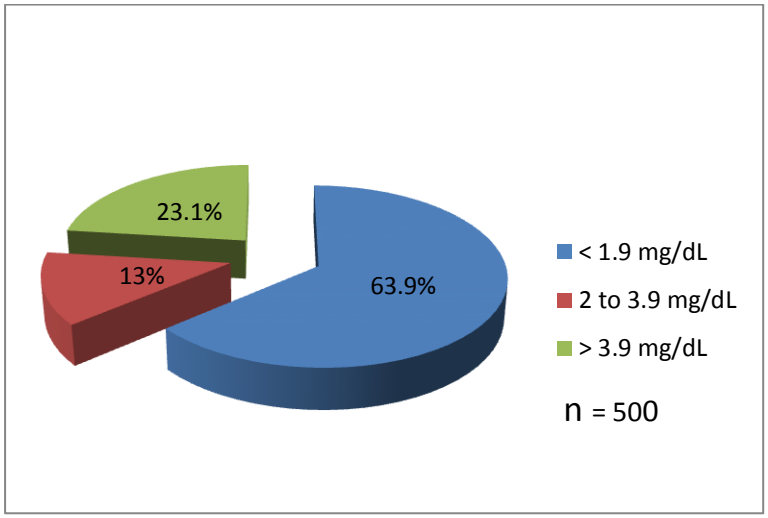
The majority of the patients (65.6%) did not have any comorbid illness but about 29.6% of the population had diabetes, hypertension or both. There was a small population with other conditions like Tuberculosis, Sickle cell anaemia, Thalassemia, Hereditary spherocytosis and Iron deficiency anaemia.

Fig.9: The personal habits of the patients



The above graph showed majority of the patients (87.6%) did not have any addictions to alcohol, smoking or tobacco intake.

Fig.10: Total bilirubin values



The total bilirubin values were less than 1.9 mg/dL in 63.9% of the study population, 13% upto 3.9 mg/dL and only 23.1% had a value above 3.9 mg/dL.

Fig.11: SGOT values

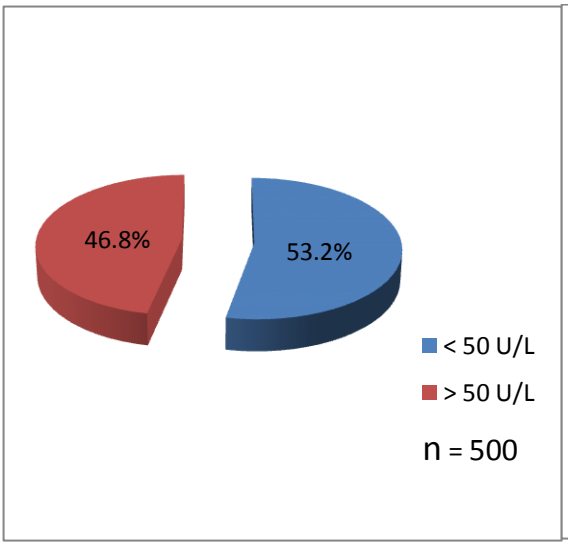
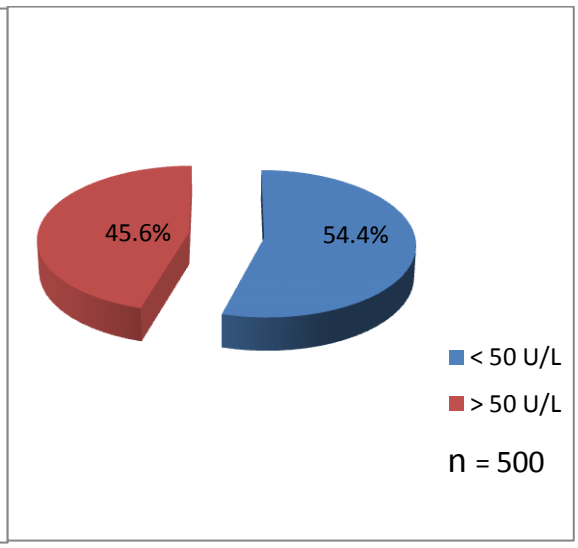


Fig.12: SGPT values



The synthetic functions of liver as reflected in SGOT and SGPT were normal in majority of the patients. The values were less than 50 U/L in 53.2% and 54.4% for SGOT and SGPT respectively.

Fig.13: Alkaline phosphatase

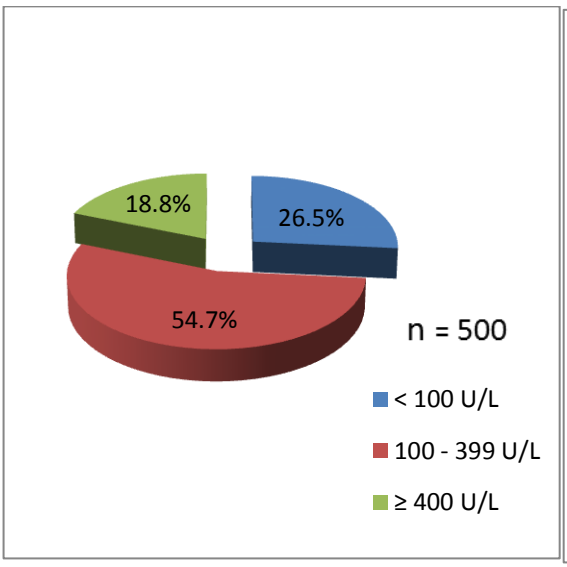
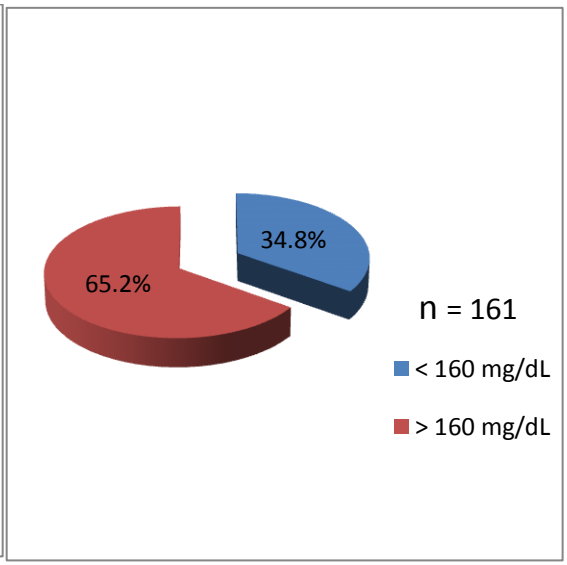


Fig.14: Total cholesterol



The serum alkaline phosphatase was elevated in majority of the patients. It was elevated in the range of 100 to 399 U/L in 54.7% and above 400 U/L in only 18.8% of the study population. It was below 100 U/L in 26.5%. The total cholesterol was elevated above 160 mg/dL in 65.2%.

Fig.15: The parameters screened by Ultrasonography

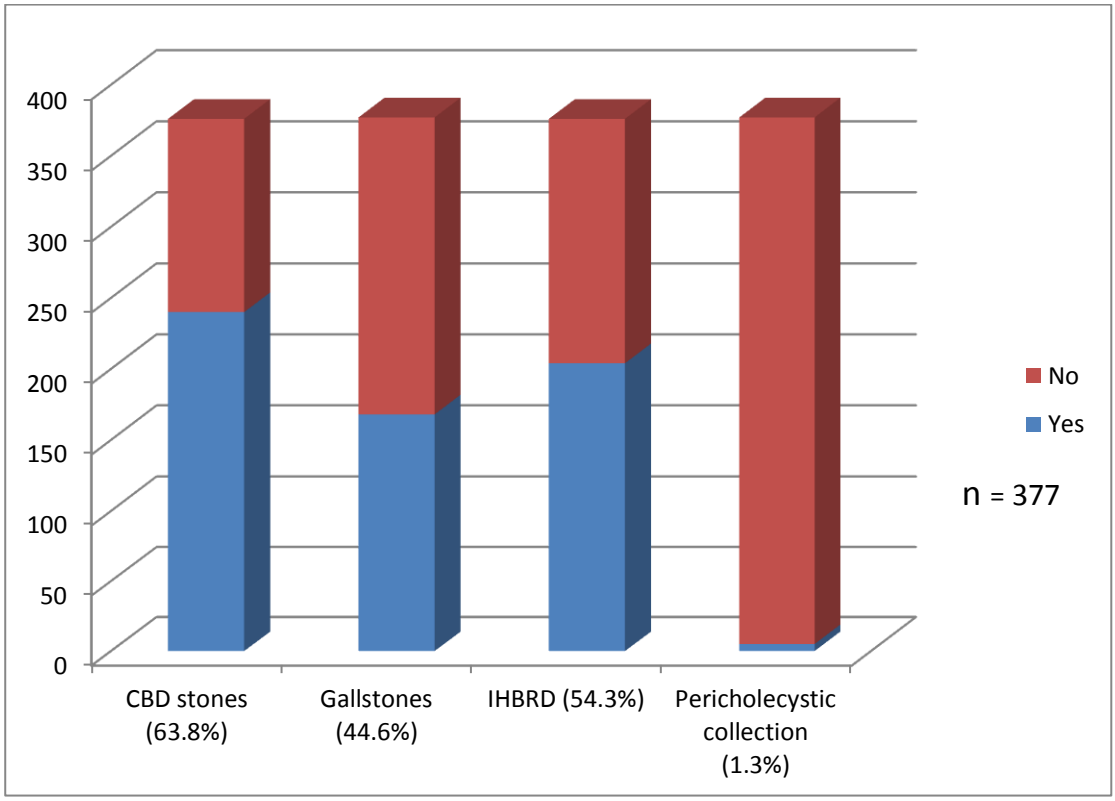
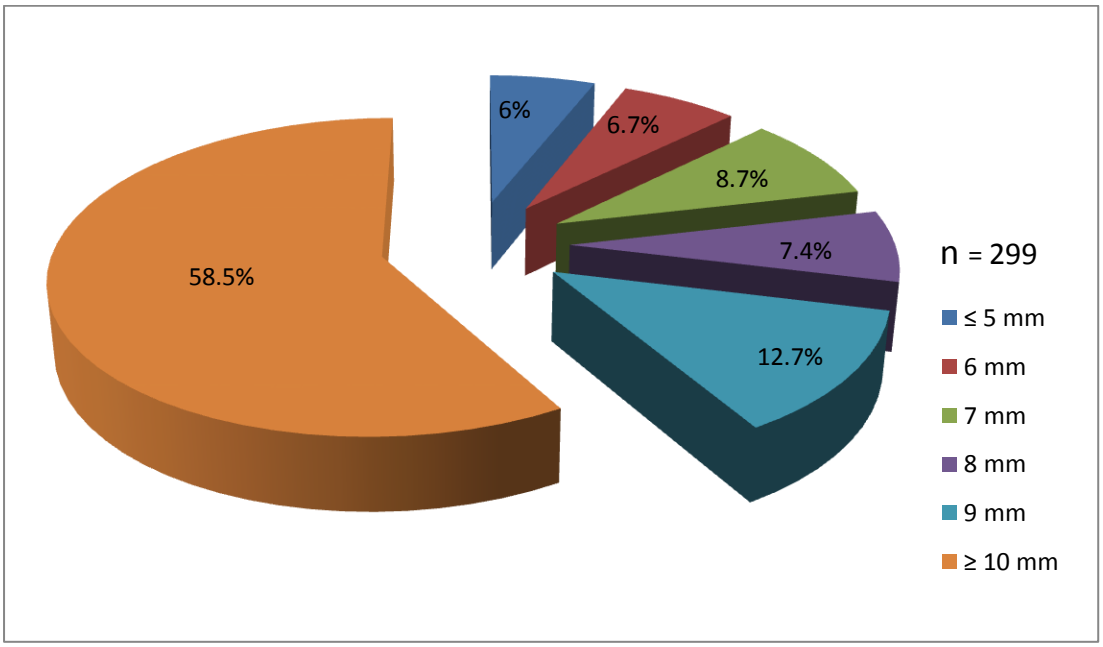


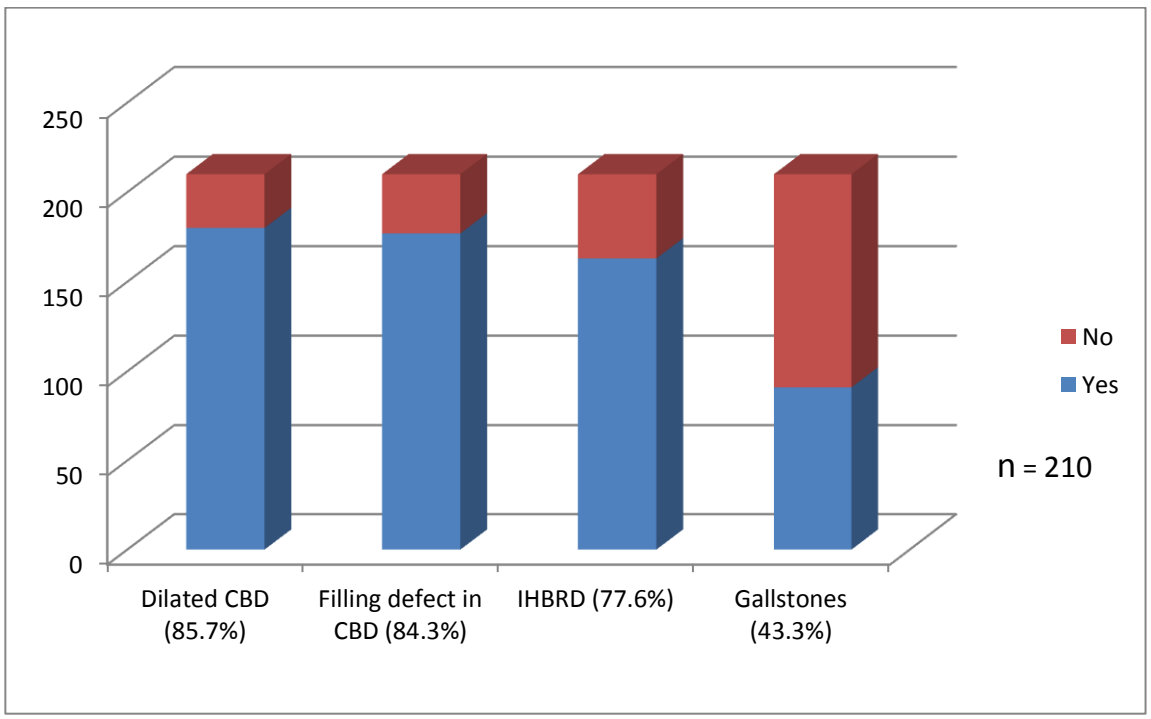
Fig.16: The common bile duct diameter measured by USG



The abdominal ultrasonography was able to screen CBD stones in 63.8% of the population screened. It showed IHBRD in 54.3% and gallstones in 44.6% of the population. There was only 1.3% of the population with pericholecystic collection.

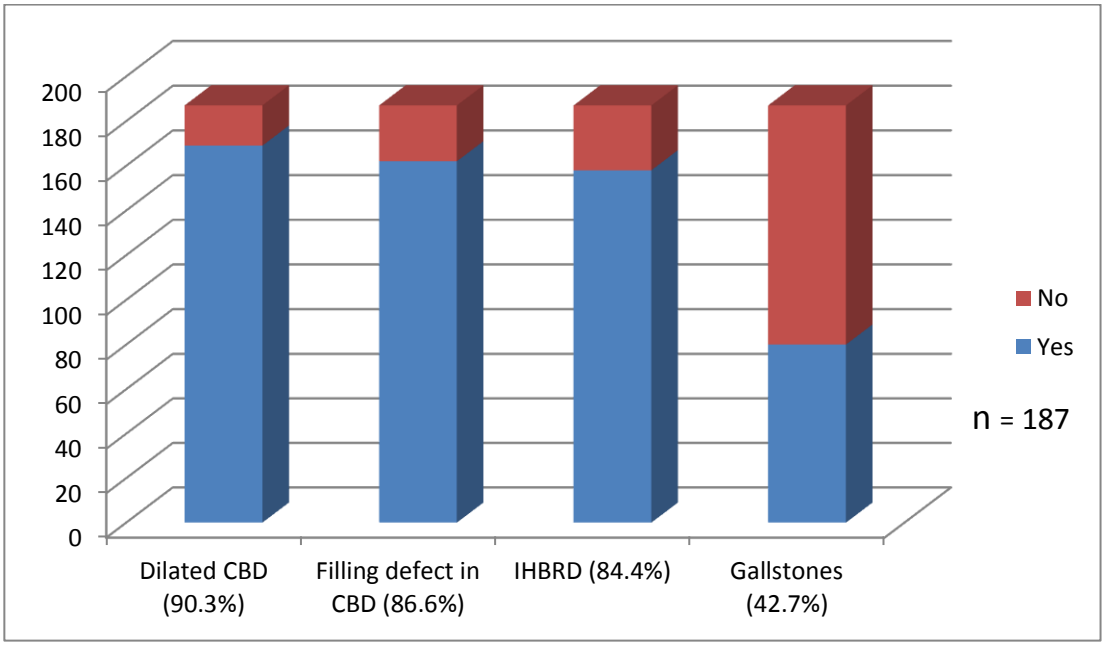
The abdominal ultrasound was able to measure the CBD size and a majority of the study population (58.5%) had a size greater than 10mm.

Fig.17: The parameters screened by CT scan



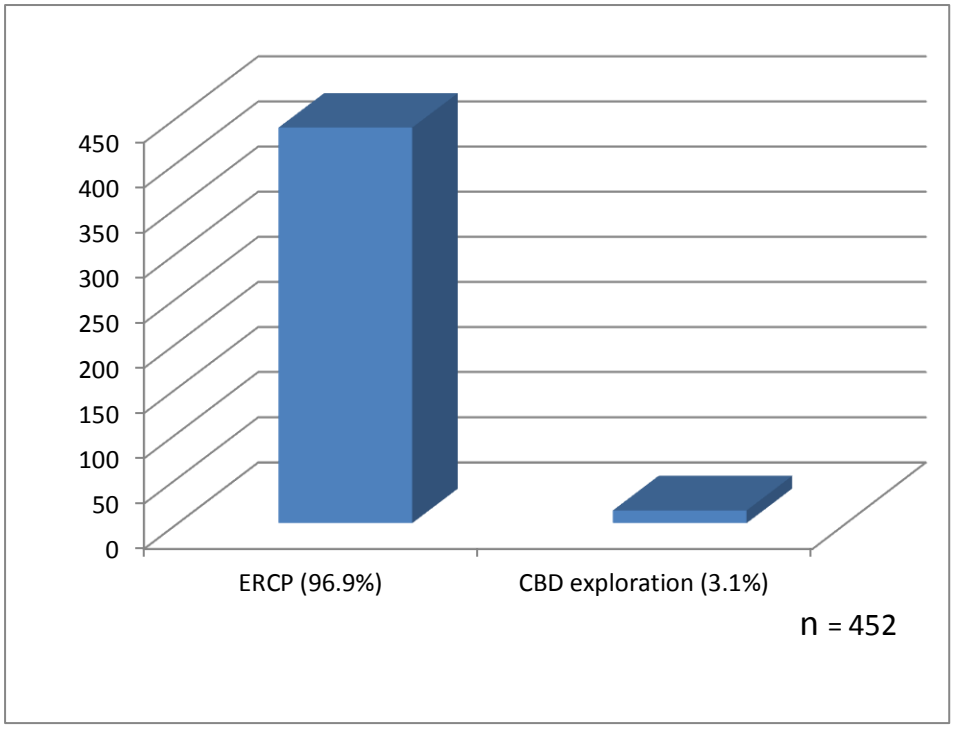
The CT scan of the abdomen detected dilated CBD in 85.7%, IHBRD in 77.6% and filling defect in 84.3%.

Fig.18: The parameters screened by MRI



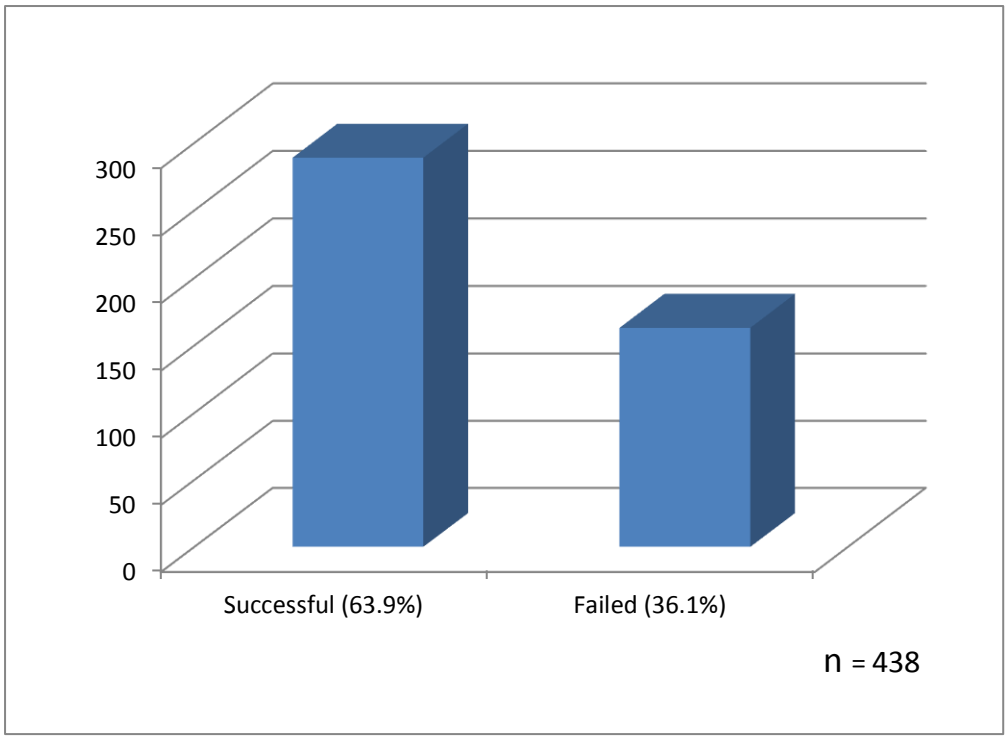
The MRI scan detected dilated CBD in 90.3%, IHBRD in 84.4% and filling defect in 86.6% of the screened population.

Fig.19: The primary intervention



A vast majority of the study population (96.9%) underwent ERCP as the primary modality of treatment and the remaining underwent direct CBD exploration as they were suspected to have underlying choledochal cyst or hepatolithiasis in addition.

Fig.20: Rate of successful clearance of ERCP



ERCP was successful in 63.9% of the study population and the rest had to undergo a secondary procedure like CBD exploration or drainage procedure. Among those who had successful ERCP clearance, 74.8% had it cleared in the first attempt, 19.1% in the second and 6.1% required more than two attempts, and some even upto six attempts. Almost all of them had a CBD diameter of more than 10mm.

Tab.6: Correlation of jaundice and the outcome of ERCP

Jaundice n = 438	Successful ERCP n (%)	Failed ERCP n (%)	Significance
Yes	107 (53.2%)	94 (46.8%)	**P** – 0.001
No	171 (72.2%)	66 (27.8%)	

The above table shows a significant correlation between the presence of jaundice and the failure rate in ERCP.

Fig.21: Correlation of total bilirubin in patients with jaundice

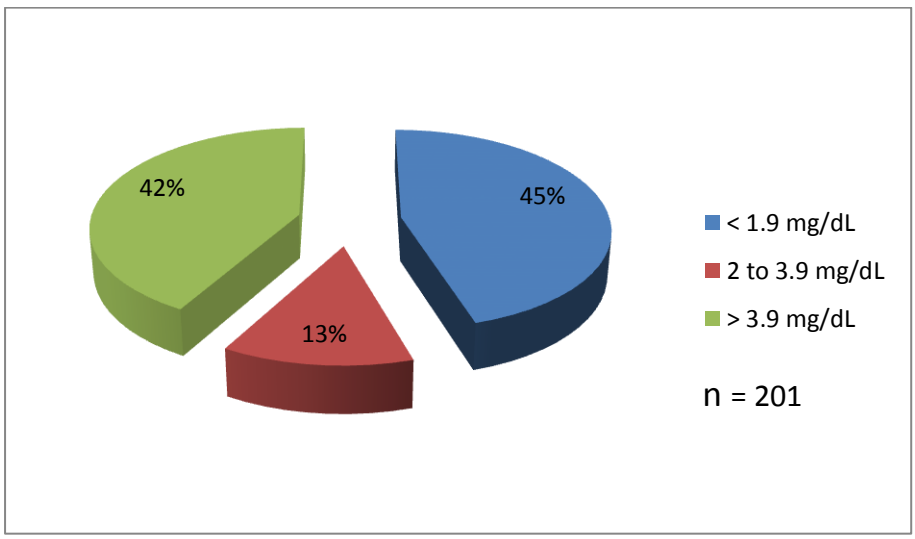
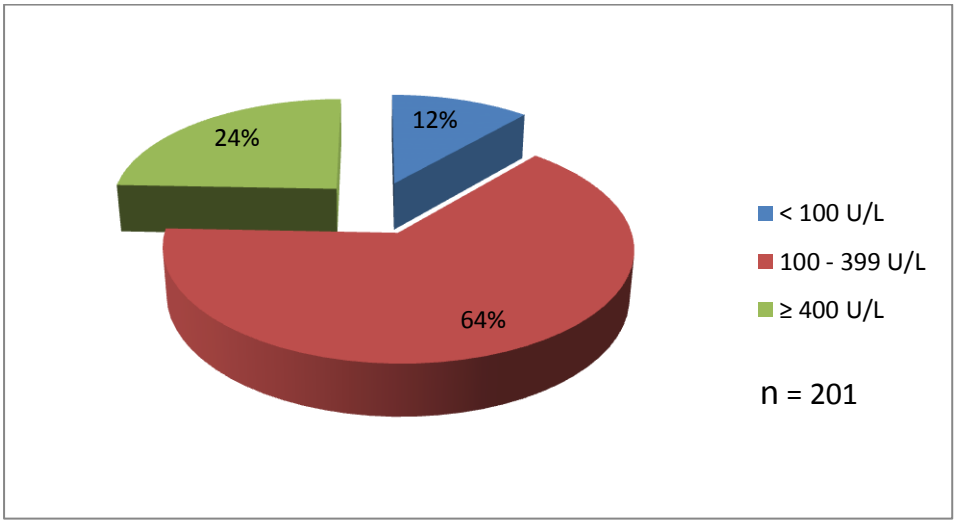


Fig.22: Correlation of Alkaline phosphatase in patients with jaundice



The above pie charts show the biochemical correlation of total bilirubin and alkaline phosphatase with jaundice.

It was noted that a majority of patients with jaundice (42%) had an elevated total bilirubin of more than 3.9 mg/dL.

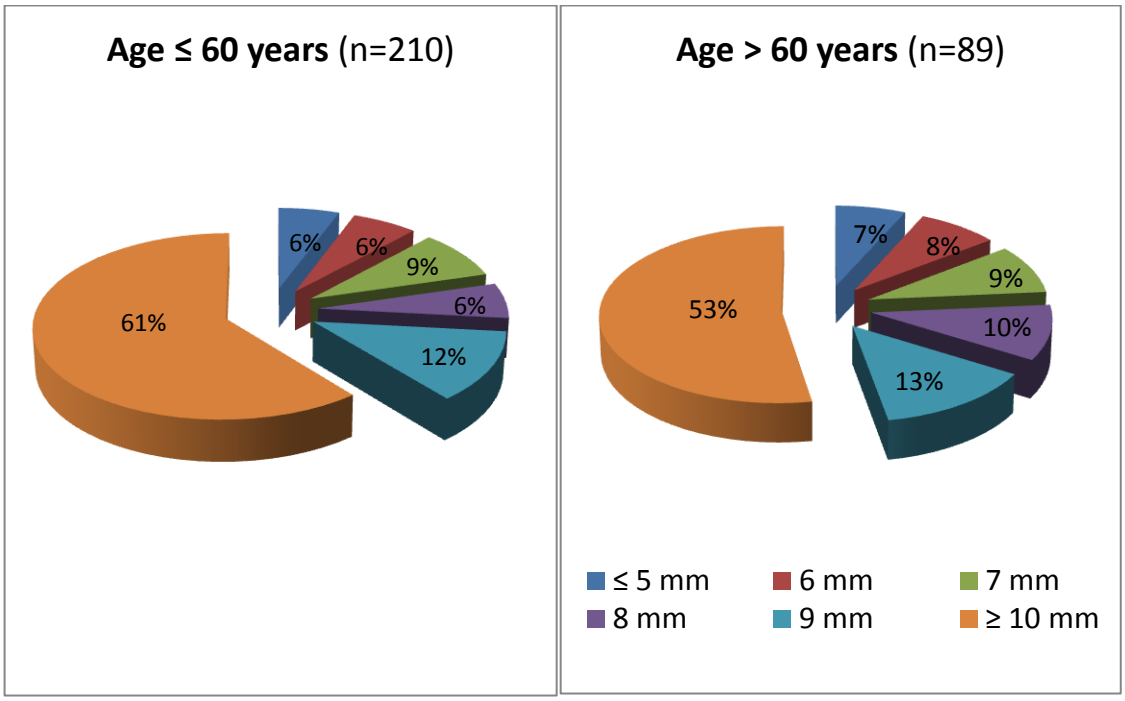
The alkaline phosphatase value in patients with jaundice ranged from 100 to 399 U/L in majority of the patients (64%).

Tab.7: CBD diameter and its correlation with ERCP outcome

ERCP	Total number	Mean CBD diameter	Standard deviation	Standard error Mean	Significance
SUCCESSFUL	143	11.179	4.9722	0.4158	**p** – 0.039
FAILED	100	12.484	4.6009	0.4601	

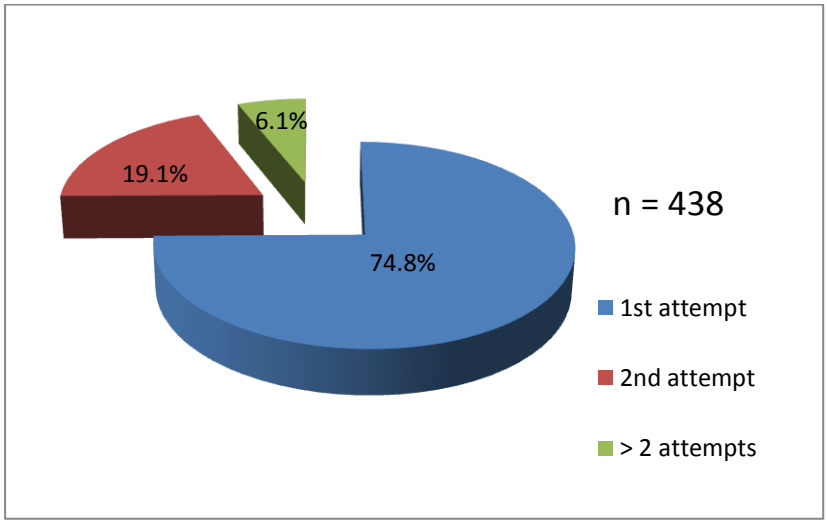
This table shows the significant correlation between the CBD diameter and the successful outcome of ERCP.

Fig.23: Correlation of CBD diameter with Age



The above pie chart shows the correlation between the CBD diameter and the age of the patient. There was no significant association noted between the age and the CBD diameter in this scenario (p value – 0.8).

Fig.24: The number of attempts



Tab.8: The number of attempts and ERCP outcome

Number of attempts n = 438	**Successful ERCP n (%)**	**Failed ERCP n (%)**	**Significance**
≤ 2	265 (95.3%)	146 (91.2%)	**P** – 0.08
≥ 3	13 (4.7%)	14 (8.8%)	

There above table shows a partial significance between more than three attempts and failure of ERCP.

Tab.9: Cholecystectomies and ERCP outcome

<table>
<tr><td rowspan="4">Successful ERCP</td><td rowspan="2">Cholecystectomy before ERCP</td><td colspan="2">Laparoscopic</td><td>42 (9.6%)</td></tr>
<tr><td colspan="2">Open</td><td>52 (11.9%)</td></tr>
<tr><td rowspan="2">Cholecystectomy after ERCP</td><td colspan="2">Laparoscopic</td><td>52 (11.9%)</td></tr>
<tr><td colspan="2">Open</td><td>33 (7.5%)</td></tr>
<tr><td>Failed ERCP</td><td colspan="3">CBD exploration / Drainage procedures</td><td>102 (23.3%)</td></tr>
<tr><td rowspan="2">Lost to follow up</td><td>Successful ERCP / Advised Laparoscopic Cholecystectomy</td><td>99 (22.6%)</td><td rowspan="2">157 (35.8%)</td></tr>
<tr><td>Advised CBD Exploration</td><td>58 (13.2%)</td></tr>
<tr><td colspan="4">Total</td><td>438</td></tr>
</table>

The above table gives the overall outcome following an ERCP. About 35.8% did not undergo cholecystectomy or bile duct exploration after the primary intervention.

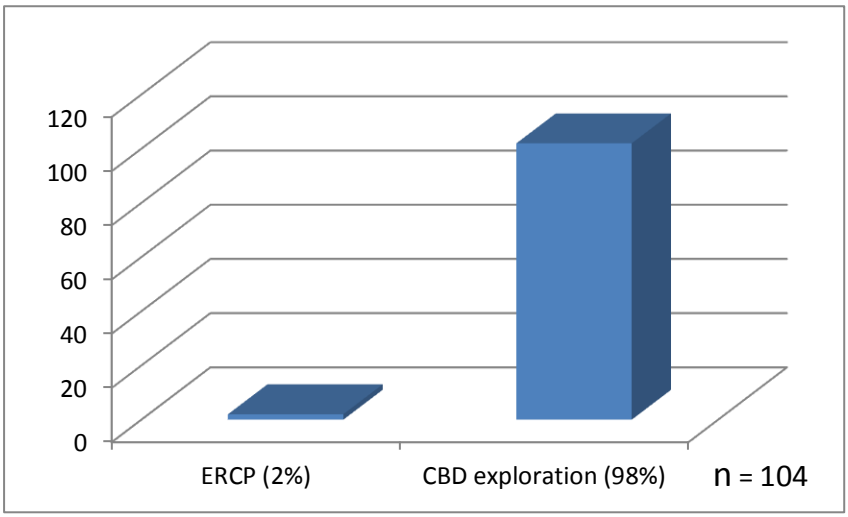
There was also a major group (21.5%) which had undergone either open or laparoscopic cholecystectomy prior to their presentation with CBD stones.

Tab.10: Successful laparoscopic cholecystectomy following ERCP

Successful ERCP proceed cholecystectomy (n = 85)	**Successful Laparoscopic cholecystectomy**	52 (61.3%)
	Laparoscopic converted Open cholecystectomy	30 (35.2%)
	Open cholecystectomy	3 (3.5%)
Total		85

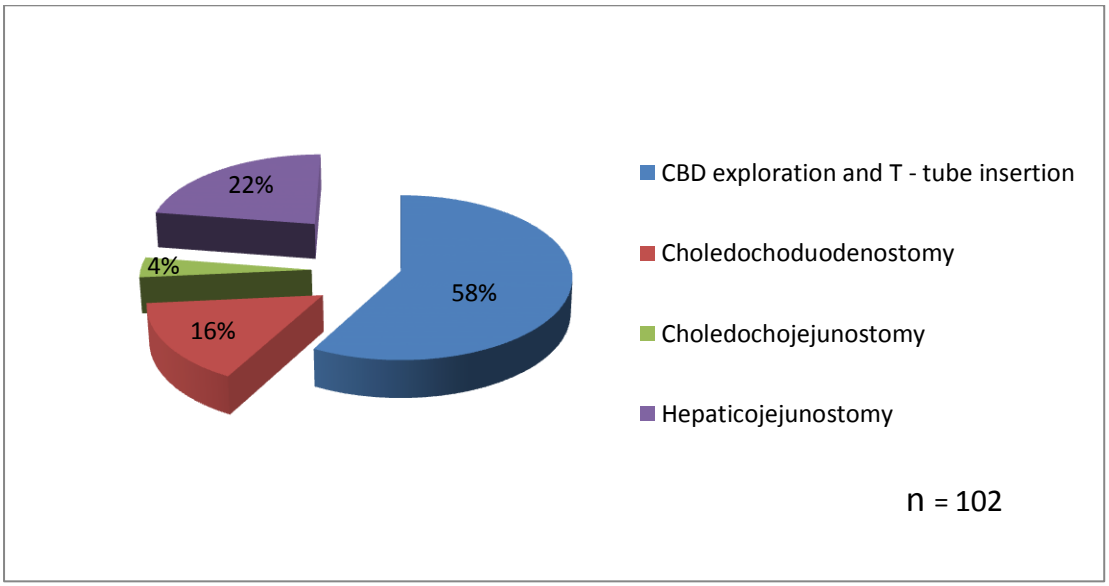
The above table shows that almost a third of the patient who underwent laparoscopic cholecystectomy following a successful ERCP had to be converted to open procedure due to failure to define the Calot's anatomy and due to dense adhesions.

Fig.25: Secondary intervention



Among those who failed primary intervention of ERCP, 98% underwent a successful CBD exploration. There were sometimes temporary drainage procedures like percutaneous transhepatic biliary drainage (PTBD) done which was followed by a definitive procedure like CBD exploration. There was a small number (2%) who had undergone CBD exploration and presented with recurrent/residual CBD stones, and required ERCP for CBD stones extraction.

Fig.26: Secondary procedures with open CBD exploration



Among the patients who underwent open CBD exploration, 58% had stone extraction and T-tube insertion, 22% had hepaticojejunostomy, 16% had choledochoduodenostomy and 4% had choledochojejunostomy.

The main reasons for proceeding to hepaticojejunostomy were intraoperative finding of choledochal cyst (7 patients), scarred or deformed duodenum (4

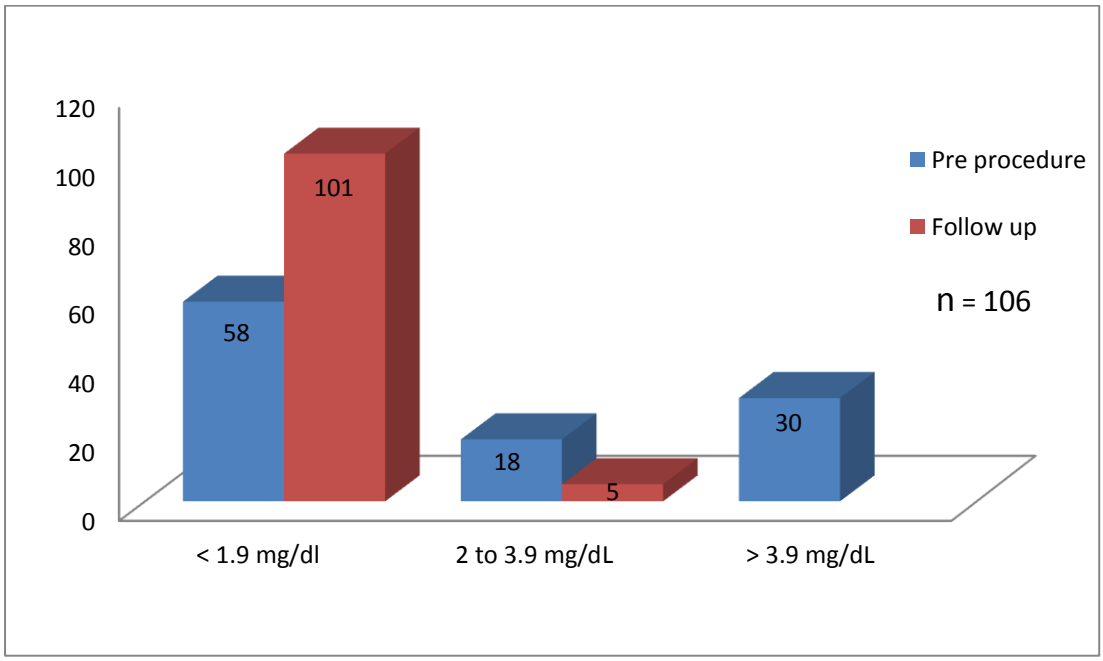
patients), large dilated CBD with impacted stones (4 patients), large choledochoduodenal fistula (4 patients), Mirizzi's syndrome (3 patients) and mid CBD stricture (1 patient).

The reasons for proceeding to choledochoduodenostomy were mainly dilated CBD with multiple stones (16 patients) and for choledochojejunostomy were large stone with distal obstruction or distal duodenal deformity (4 patients).

The other procedures which accompanied were sphincteroplasty (2 patients) and liver biopsy (2 patients).

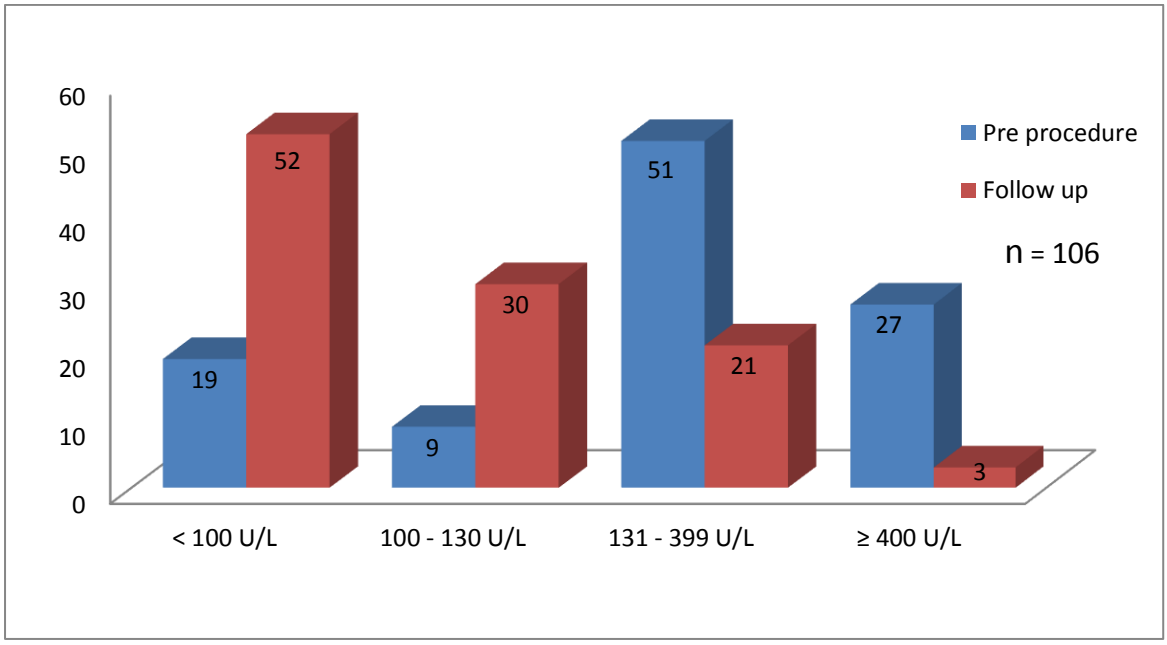
The patients on follow up were studied for the return to normalcy in their selective liver function tests and radiological imaging.

Fig.27: Total bilirubin values on follow up



There was a drop in the total bilirubin value to normal in most of the patients. There were none in the follow up group with a value greater than 3.9 mg/dL. Among the 5 patients with a value from 2 to 3.9 mg/dL, (one had undergone open CBD exploration and the remaining four had undergone initially an ERCP). The one patient, who had the open CBD exploration, was found to have non-alcoholic steatohepatitis with cirrhosis and a normal CBD on abdominal ultrasound. Among the 4 who had ERCP, one patient was suspected to have a stricture and was advised further imaging with EUS/MRCT but did not come for further follow up. One patient had recurrent stone and underwent ERCP and successful stone extraction. Two of the remaining were found to have only indirect hyperbilirubinemia with normal CBD on abdominal ultrasound.

Fig.28: Alkaline phosphatase on follow up



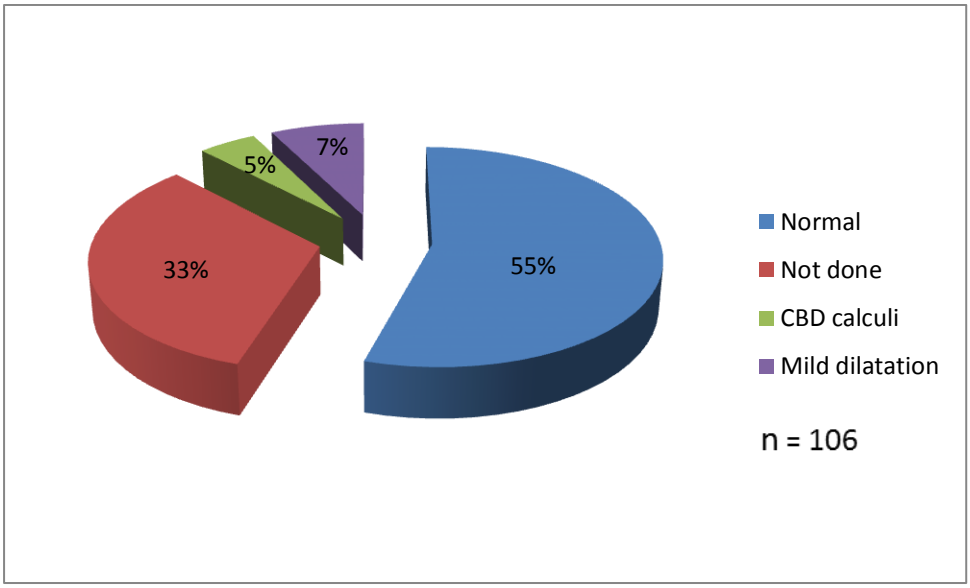
The serum alkaline phosphatase also showed similar trends towards normal range. Three patients had a value more than 400 U/L, (One of them had undergone open CBD exploration and the remaining two had undergone ERCP). The patient who had undergone open CBD exploration was found on evaluation by MRCT scan to have probably a terminal bile duct growth and was advised side viewing scopy but was discharged at request. Among the remaining two patients, one of them as described above was advised further imaging with EUS/MRCT but did not follow up. The other patient had recurrent CBD stone and advised CBD exploration.

Among the 21 patients with a follow up value ranging from 131 to 399 U/L, (12 had undergone open CBD exploration and 9 had undergone ERCP). 13 of them (8 following open CBD exploration and 5 following ERCP) had normal CBD with no calculi on the abdominal ultrasound, so were advised follow-up.

Among the remaining, from the open CBD exploration group (4), one had a left hepatic duct stone and underwent open cholangioscopy and extraction of left hepatic duct calculus. The remaining three were suspected to have stricture, one of whom underwent HIDA scan which showed no hold up, so was advised to follow up. The other two were advised redo hepatico-jejunostomy.

Among the remaining 4 patients from the ERCP, two of them had recurrent stones and underwent ERCP and stone clearance. One of them was suspected to have portal biliopathy as repeat ERCP was normal. The other underwent laparoscopic cholecystostomy and was on follow up.

Fig.29: Follow up Abdominal Ultrasound scan



Among the patients who had follow-up, there were 55% with normal trans abdominal ultrasound findings of normal size CBD without any stones. There were 7% of these patients (4 had undergone open CBD exploration and 4 had undergone ERCP) who had mildly dilated CBD measuring around 10mm and 5% of the patients (one had undergone open CBD exploration and 4 had undergone ERCP) had recurrent CBD stones, which were managed as described above. The remaining 33% did not have any follow up scan and the liver function tests of these patients were within normal limits.

Among the entire population there were two mortalities. Both patients succumbed to the septic complications following the procedure done. One of them had undergone open CBD exploration and developed bile leak and the other patient had undergone ERCP and had acute cholangitis.

Chapter 6

ANALYSIS

The total number of patients studied was 500.

There was almost equal distribution of male to female ratio, showing no sex predilection for choledocholithiasis, although female gender is a risk factor for gallstones.

The age group of patient ranged from 18 years to 89 years with a mean age of 52 years, signifying that choledocholithiasis can occur early in life but predominantly affects the middle aged.

The population distribution was predominantly in the eastern states and more in the Bengali community. This was also shown earlier in a population based study on choledocholithiasis in various Indian population (4).

The average body mass index in the study population was 22.15, which falls in the normal range.

Among the various clinical presentations, abdominal pain was the commonest presenting complaint which was recorded in 76% of the patients. Following this was jaundice which was seen in 45.4% of patients. The other

symptoms like pruritus, pale coloured stools, dark coloured urine and anorexia were recorded in 10% of the study population.

The complications of choledocholithiasis like ascending cholangitis and pancreatitis was recorded 25.4% and 5.4% respectively. This rate was high but could be expected due to a referral bias being a tertiary care centre.

About 30% of the study population was either hypertensive or diabetic or both. There were a small number with haemolytic disease like hereditary spherocytosis, thalassemia and sickle cell anaemia. Majority of the patient had no comorbid illnesses.

Few of the patients had icterus on general examination but there were no significant findings on abdominal examination.

On blood investigation the commonest abnormality noted in the liver function test was an elevated alkaline phosphatase. The serum alkaline phosphatase in majority of the patients were elevated, in the range between 100 U/L to 399 U/L, which was greater than normal. The other parameter which was elevated was the total cholesterol, noticed to be above 160 mg/dL in 65% among the tested population. There was no significant difference noticed in the other laboratory parameters. Yang et al. showed that total bilirubin had the highest specificity of 87.5% to predict common bile duct

stone. They also concluded that total bilirubin, SGOT, SGPT and alkaline phosphatase had high negative predictive value (130).

The most common radiological finding in trans-abdominal ultrasound was the dilated common bile duct. It was noted that 87.3% of patients had a CBD diameter more than 7mm and 58.5% had a diameter more than or equal to 10mm. The age cut off of 60 years did not reveal significant difference in the CBD diameter, which suggests the dilatation was independent of age (p value – 0.78).

The CT scan of the abdomen also revealed a dilated CBD in 85.7% of the study population followed by filling defect in the common bile duct and IHBRD. A similar screening pattern was seen in the MRI study of the abdomen. But overall MRI had the highest sensitivity in picking up a CBD stone.

Following the diagnosis of choledocholithiasis, a major group of the study population (96.9%) underwent ERCP and clearance of the stone. The failure of which, as seen in 36.1% of the patient, had to undergo a temporary drainage procedure like percutaneous transhepatic biliary drainage or a definitive procedure like CBD exploration (23.3%) and the remaining were lost to follow up. There was a small number which underwent primary CBD exploration (3.1%) due to already attempted ERCP at another centre or due to associated hepatolithiasis.

The leading cause for failure among the ERCP group was large stones followed by multiple stones. There were also other important factors like abnormal anatomy due to deformed duodenum, periampullary diverticulum and few due to technical difficulty and uncooperative patient.

Most times (74.8%) the stone was extracted in the first attempt. When there was more than two attempts the chance of failure was borderline significant (p value – 0.08).

Analysis was done to correlate clinical, biochemical and radiological features to the successful clearance of the common bile duct stone.

A two proportions test (Z-test) was done to correlate jaundice and outcome of ERCP, and it was found to have a higher failure rate in the presence of jaundice (p value – 0.0002). Similarly there were significant failure rates in those with cholangitis (p value – 0.002) as compared to those with pancreatitis (p value – o.246).

There was no gender predilection or significant correlation between comorbid illnesses and personal addictions to the outcome of ERCP.

The abdominal ultrasound measurement of the CBD diameter (mean diameter – 12.484mm) was found to be significant (p value – 0.039) in the group with failed ERCP as compared to those with successful ERCP.

The patients who underwent laparoscopic cholecystectomy following a successful clearance of CBD stones by ERCP, had a conversion rate of around 35.8%. The routine conversion rate was about 5% (131). Morshed et al. showed that the conversion rate following an ERCP is 13.3% if performed after 72 hours and it increases to 33.3% if after a week (132). The majority of the secondary intervention was by CBD exploration. A small number presented with recurrent CBD stones following CBD exploration (3%), who underwent ERCP and stone clearance.

Majority of the study population was lost to follow up and only about 20% had regular follow up data. The reason could be that they were well post procedure, the long waiting period of 8 to 10 weeks prior to operation or could be the geographic distance and difficulty in coming for a follow-up.

Follow up of the patients showed that the total bilirubin had begun to normalise in majority of the patients (95.3%). The abdominal USG revealed no stones in CBD except in four patients (5%) who had a recurrent/residual stone which was removed by ERCP. The CBD size also was normal except in 7% who had mildly dilated CBD about 10mm. There were two mortalities following septic complications post procedure.

Chapter 7

CONCLUSIONS

- The most common clinical presentation of choledocholithiasis was abdominal pain.
- Abdominal ultrasonography was an effective initial investigation to indicate the presence of choledocholithiasis.
- MRI was most sensitive to demonstrate CBD stone.
- ERCP was the preferred primary intervention at this institution.
- Absence of jaundice was an important predictor for a successful outcome of ERCP.
- More than two attempts at ERCP predicted a higher failure rate in complete stone clearance.
- Common bile duct diameter more than 12.5mm showed a significantly higher failure rates in ERCP and stone clearance.
- Delayed laparoscopic cholecystectomy following ERCP could lead to a higher conversion rate.
- Common bile duct exploration was the preferred intervention following failure of primary intervention.
- Alkaline phosphatase was a better predictor of outcome on follow up.

Chapter 8

LIMITATIONS

- The data quality relies on accuracy of written record or recall of individuals also termed as recall bias.
- All the important data was not available and the missing data had to be excluded, reducing the strength of this study.
- The financial constraints played an important role in the management of the patients.

Chapter 9

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Chapter 10

ANNEXURES

9.1.0. Performa

Name: Serial No:

Hospital No: Married:

Age: Place:

Sex: BMI:

Clinical symptoms:

1. History of cholangitis (present / absent)

2. Acute pancreatitis (present / absent)

3. Dark urine (present / absent)

4. Pale colored stools (present / absent)

5. Pruritus (present / absent)

Clinical signs:

1. Icterus (present / absent)

2. Abdominal tenderness (present / absent)

3. Palpable gall bladder (present / absent)

Biochemical findings:

1. Serum Bilirubin <1.9, 2.0 – 3.9, and >4.0

2. Serum Alkaline phosphatase < 100, 100 - 399, >400

3. Liver enzymes (SGOT/SGPT) < 50 and >50

Radiological findings:

USG Presence of choledocholithiasis (present / absent)

Size of common bile duct 5mm or less, 6mm, 7mm, 8mm, 9mm, 10mm or more

Presence of intrahepatic biliary dilatation (present / absent)

Presence of cholelithiasis (present / absent)

CT scan Bile duct dilatation (present / absent)

Presence of filling defects in Common bile duct (present / absent)

Cholelithiasis (present / absent)

MRI Scan Bile duct dilatation (present / absent)

Presence of filling defects in Common bile duct (present / absent)

Cholelithiasis (present / absent)

Endoscopic ultrasound Bile duct dilatation (present / absent)

Presence of filling defects in Common bile duct (present / absent)

Cholelithiasis (present / absent)

Treatment: Primary treatment ERCP/ common bile duct exploration

Failure of pre-treatment - abnormal anatomy (Y/N), large size stone (Y/N),

multiple stones (Y/N), Others

Follow up: Serum Bilirubin <1.9, 2.0 – 3.9, and >4.0

Serum Alkaline phosphatase < 100, 100 - 399, >400

Liver enzymes (SGOT/SGPT) < 50 and >50