



ROLE OF IMAGING MODALITIES IN DIAGNOSIS, MANAGEMENT AND FOLLOW UP OF CHOLECYSTOLITHIASIS IN NCR REGION OF INDIA

Radiodiagnosis

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ABSTRACT

HISTORY –Gall bladder Calculi are most common worldwide problem, more prevalent in developing country like India (NCR region). In the Developed countries, 10 to 15 % of adults have gall stones. Most people with Gall Stones (about 80%) are asymptomatic. The world Society of Emergency surgery developed extensive guidelines to deal with this disease which causes significant morbidity and mortality. Most of the cases are diagnosed as asymptomatic gall bladder calculi on the basis of clinical examination and abdominal ultrasonography. Besides this, asymptomatic gall bladder calculi are also detected on routine Ultrasonography of abdomen for other causes.

There is a definite role of imaging modalities in detection of Gall bladder Calculi and related diseases, & their complications like cholecystitis, Pancreatitis, Obstructive Jaundice & Cholangitis, Choledocholithiasis, along with management in deciding types of treatment which may be conservative versus surgical (laparoscopic /or open cholecystectomy) and in post-operative follow up cases also (1).

Among the surgery category, there are two methods, available such as laparoscopic cholecystectomy versus open cholecystectomy for removal of Gall bladder calculi which is decided on the basis of clinical, laboratory tests and ultrasound /or other imaging modalities report's findings by consulting surgeon. (2)

Ultrasonography plays an important role in most of the patients of Cholelithiasis with or without cholecystitis (acute or chronic) and follow up of post operated cases to avoid any complications. (3)

Although other imaging methods like CT scan, MRCP, EUS, PET-CT and Scintigraphy are indicated for high risk patients when Gall bladder Calculi are associated with complications like empyema, large Polyp, Mucocoele of Gall Bladder, malignancy of Gall Bladder, CBD mass and hepatic/ Lymph Nodal metastases.

Oral Dissolution therapy and ESWL (Lithotripsy) therapy is usually advised in rare cases where successful surgery is not possible in management of cholelithiasis.

Laparoscopic Cholecystectomy remains the surgical choice for symptomatic cholecystolithiasis (Gall Stones with inflammation of GB)

Percutaneous Cholecystostomy is an alternative method for critically ill patients with emphysema GB and sepsis.

Now a days, Role of Interventional Radiology is becoming more popular in aspiration of post-operative collection, Mucocoele / empyema of Gall bladder and therapeutic role of ERCP in Distal CBD Calculus removal.

Follow up ultrasound is advised to rule out any biliary leak /or collection.

AIMS AND OBJECTS ---To Evaluate the role of imaging particularly ultrasonography Abdomen and other modalities in detection of Gall Bladder Calculi & related pathology and decide to select the method of treatment—conservative or surgical (laparoscopic Cholecystectomy versus open cholecystectomy) and post-operative follow up.

MATERIAL AND METHODS —It is RETROSPECTIVE study of 300 patients of gall bladder calculi & related pathology diagnosed on initial Abdominal Sonography aged between 20 to 60 years. 254 patients were selected for operation during 01 September 2018 to 11 February 2020, at tertiary hospital of G.S. Medical college in sub-urban area within NCR.

The total 300 patients were divided on the basis of types of treatment into five groups:-

(1). Conservative management of asymptomatic cases / unfit for operations (46 cases),

(2). Selection of Cases for Laparoscopic Cholecystectomy (168 cases)

(3). Selection of cases for open surgery (Cholecystectomy) -76 cases

(4). Decision of cases for conversion surgery (10 cases)

(5) Post-Operative follow up of almost all cases before discharge from the hospital.

Usually Surgeon advised to opt for laparoscopic surgery as compared to open surgery option which is decided by surgeon after consultation with Patients by explaining pros and cons of each method.

RESULTS --- out of the 300 patients selected for treatment of gall bladder calculi, 168 (56 %) cases were operated by Laparoscopic cholecystectomy while 76 (25.3 %) were selected for open cholecystectomy, 10 (3.33%) cases were converted for conversion surgery and remaining 46 (15.3%) cases were advised for conservative treatment.

CONCLUSION —Now a days, there is a major role of diagnostic imaging procedures, like ultrasonography, EUS and C.T scan Abdomen, MRCP and ERCP, PET-CT Scintigraphy, Interventional Radiology in diagnosing, management (Conservative versus Surgical—laparoscopic / or open cholecystectomy) and post-operative Follow up in Gall bladder Calculi (cholelithiasis) and GB related other pathological conditions.

Laparoscopic Cholecystectomy is the efficient method of surgical choice for acute calculous cholecystitis, not only in INDIA but Worldwide too.

KEYWORDS

Gall Bladder Calculi (stones), Cholelithiasis, Cholecystitis, Cholecystolithiasis, and Laparoscopic Cholecystectomy. Acute Cholecystitis with Cholelithiasis, Calculous Cholecystitis, Open Cholecystectomy, conversion surgery, bile duct injury, ERCP (Endoscopic Retrograde cholangio-pancreatography), MRCP (magnetic Resonance cholangio-pancreatography), Choledocholithiasis (CBD calculus/ calculi), Cholangitis, IHBRD (Intrahepatic biliary Radicle dilatation)

INTRODUCTION / BACKGROUND —

Gall Bladder Calculi (cholelithiasis) are a major health problem in NCR of India and in other developing countries worldwide. It is a most common gastro-intestinal disorder for which patients are admitted in hospitals.

The vast majority of gall bladder Calculi (80% appx) are asymptomatic or presented with vague pain in abdomen and are diagnosed by ultrasonography of the Abdomen.

However 15 to 20 % of Gall bladder calculi cases are associated with

symptoms like pain in abdomen (RUQ), nausea and vomiting & required treatment.

The symptomatic manifestation in s of Gall bladder calculi are variable and ranging from mild to severe biliary colic, presented in acute calculous cholecystitis or (Cholecystolithiasis) (5).

In developing countries like India, 10 -15% of adult population (20-60 years) of both sexes, (Females are more prone) to develop cholelithiasis.

Biliary colic occurs in 10 to 20 % conservative (medically) treated cases of Gall bladder Stones on follow up ultrasound abdomen.

In cases of patients discharged without surgical treatment , the probability of biliary colic related to G B Calculi are 3 % in 3 months , 6% in 6 months and 12 % within a year.

For this reason, once the symptoms are developed, the patients must be advised for surgical removal of Gall Bladder (cholecystectomy) to avoid complications in future .

The detailed clinical history and appropriate laboratory tests and ultrasound abdomen are sufficient to diagnose cholelithiasis with Acute Cholecystitis accurately.

Laparoscopic Cholecystectomy has become the treatment of choice for Acute, sub- acute and many chronic cholecystitis with cholelithiasis cases around the world.

In the present era, with the availability of expert surgeon with high level of competency, the complications and conversion rate has been reduced to 3.3 % only.

Patients with high probabilities of complications, surgeon must opt for open cholecystectomy so as to lessen the intraoperative and post-operative risk.

There is more pain and longer hospital stay in open cholecystectomy, while the successful laparoscopic cholecystectomy is associated with an early recovery and short hospital stay.

The treatment cost of laparoscopic cystectomy is slightly more or equal to open cholecystectomy.

IMAGING TECHNIQUES— 1. ULTRASONOGRAPHY—

This test is the one most commonly used to look for signs of gall stones(Calculi).Abdominal sonography features include single/ or multiple hyperechoic /echogenic foci with distal acoustic shadowing in gall bladder lumen.

This imaging procedure is the method of choice for detecting Gall stones.

Minimum 6 hours fasting is required for ultrasonography of abdomen which is performed in supine and left lateral decubitus ,prone and erect positions. Normal Gall bladder wall thickness is 3 mm or less, anterior wall is measured in long axis perpendicular position.

Transverse diameter of gall bladder should be less than 4 cm .There are three sonographic criteria for diagnosing Cholelithiasis ,which are echogenic focus ,cast distal acoustic shadowing with gravitational dependency and normal wall thickness .Biliary sludge is also noted in long standing cases of cholelithiasis. Sometimes Sludge balls are also noted in GB lumen and do not cast distal shadowing.

Acute Cholecystitis is diagnosed by tenderness in RUQ, associated with fever, leukocytosis or elevated CRP with classical ultrasound findings such as thickening of GB wall >3 mm ,Distension of GB lumen >4 cm ,Positive sonographic Murphy's sign , usually impacted stone in neck ,pericholecystic fluid collection and hyperemic GB wall on color Doppler .(4)

The criteria of diagnosing chronic Cholecystitis is uniform echogenic pattern of G.B.Wall Thickening ,contracted , smaller in size, Calculi in lumen ,Wall –Echo-Shadow complex (WES) as double arc shadow sign due to Contracted GB filled with stones causing distal acoustic

shadowing.

In case of Empyema of gall bladder , the patient is very ill with fever and acute pain in abdomen with fine dense echoes in bile suggestive of pus with pericholecystic GB collection ,US guided drainage is advisable before surgery Other complications of acute Cholecystitis like Gangrenous Cholecystitis ,Emphysematous cholecystitis , GB Perforation can also diagnosed by ultrasonography , which can be confirmed with CT Scan/ MRI Abdomen .

Xanthogranulomatous Cholecystitis (XGC) is diagnosed by compressed lumen ,multiple hypoechoic mural nodules with markedly thickened wall and calculi in adjacent region.

C T Scan abdomen/MRI Abdomen are other modalities for confirmation of Ultrasound findings .

Gall bladder polyps can also be diagnosed by ultrasonography of abdomen, better evaluated by CT scan/ MRI Abdomen or by EUS.

Gall Bladder carcinoma can be initially diagnosed by Mural thickening –focal, diffuse ,irregular/ or as polypoid GB Mass / or Heterogenous Gall bladder mass in GB Fossa replacing normal outline and may invading into adjacent Liver .



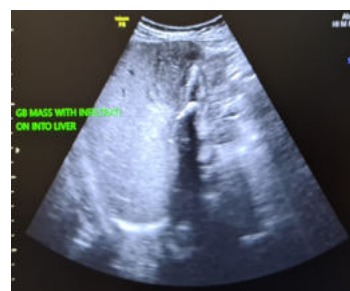
GB Calculi

Calculus Cholecystitis



Cholelithiasis

GB Mass



GB Mass with Infiltration into Liver

2.C. T. Scan Abdomen—

This test uses x rays to construct detailed images of abdominal organs with the assisted computer system .CT scan can give additional information on the bile ducts and liver which may be involved in gall bladder diseases.(5)

3. HIDA SCAN(Cholescintigraphy)—

During this test, a radioactive material called hydroxyl imino-diacetic acid (HIDA) is injected into the Patient .The material is taken up by the gall bladder, and shows how the gall bladder is functioning .This test is useful when the ultrasound report is inconclusive ,especially if there is acute inflammation of the gall bladder and the outlet of the gall bladder is blocked .It is also useful when the GB is diseased but without calculi

in gall bladder lumen (acalculous Cholecystitis).

4. Magnetic Resonance Cholangiopancreatography (MRCP)---

This test is done by using MRI to produce detailed images of biliary tree, liver, gall bladder and CBD. It is very useful to visualize calculi in the common biliary duct.

5. Endoscopic Retrograde Cholangiopancreatography (ERCP)---

In this procedure, a tube is placed down the patient's throat, into the stomach then into the small intestine. Dye is injected and the biliary ducts, gall bladder, liver and pancreas can be seen on x-ray. ERCP is now used therapeutically for calculus removal from CBD, stent placement in blocked CBD which caused pancreatitis and cholangitis.

6. Endoscopic Ultrasonography (EUS)---

This procedure is considered a superior investigation when compared to conventional ultrasonography for imaging of Gall bladder lesions as it provides high resolution images of small lesions by using high frequency probes.

EUS can be used to evaluate gall bladder diseases like suspected cases of acute cholecystitis, GB polyps, and in diagnosis & staging of carcinoma gall bladder.

Moreover, EUS-FNA is a sensitive tool for evaluation of gall bladder and liver masses.

MATERIAL AND METHODS---

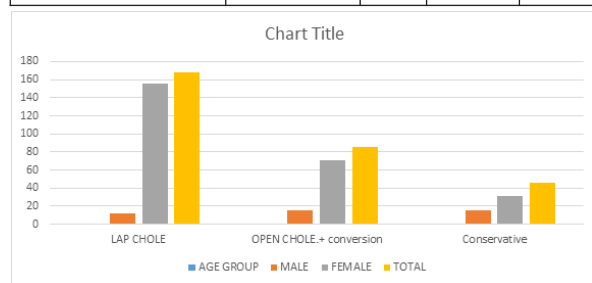
Out of 300 patients, 168 (56%) case were operated by laparoscopic cholecystectomies while 26 (25.3%) cases by open cholecystectomies, 10 (3.3%) cases by conversion surgeries and remaining 46 (15.3%) cases advised for conservative management.

186 patients were not presented with RHQ pain in abdomen and diagnosed on ultrasonography for vague abdominal symptoms like burning in epigastric region, abdominal distension after meal, and 72 patients were presented with features of acute cholecystitis with cholelithiasis, remaining 42 patients had already diagnosed earlier with past history of mild attacks of pain in abdomen. (6)

The demographic distribution of cases underwent treatment through Laparoscopic cholecystectomy versus open cholecystectomy is summarized in Table number 1 as follows:-

Table No. 1. Demographic Characteristics

	AGE GROUP	MALE	FEMALE	TOTAL
LAP CHOLE	20-60 YRS	12	156	168
OPEN CHOLE.+conversion	20-60	13+02	63+08	76+10
conservative	20-60	15	31	46



Most of the patients with gall bladder calculus/calculi were in the age group from 20 to 60 years admitted in surgery ward through OPD / emergency in our tertiary care hospital.

Many patients of elder age group were having associated comorbidities as shown in Table number 2 as follows:-

Table 2. Concurrent Comorbidities

NAME OF THE DISEASE	LAP CHOLE	OPEN CHOLE +conversion	Conservative
HYPERTENSION	38	06	04
DIABETES	26	04	08
COPD	31	03	02
ASTHMA	23	02	01

MANAGEMENT OF G B CALCULI --- the management of GB

calculi (14) are summarized in five groups as follows:-

1. CONSERVATIVE (NON SURGICAL) TYPE ---46 (15.3%) INDICATIONS---

Patient is young age and asymptomatic and free of co-morbidities
Accidentally detected GB Calculi on routine Ultrasound for other cause.

Normal functioning Gall Bladder with normal wall thickness and few mobile calculi

Calculi size less than 5 mm

Micro-cholelithiasis and long standing Echogenic Biliary sludge

Decrease life expectancy

Patient not willing for surgery

Patient unfit for anaesthesia

Asymptomatic GB Calculi in Pregnancy

2. Laparoscopic Cholecystectomy --- 60 (appx) %

Main Surgical Method Of Choice, May Be Early Versus Delayed Laparoscopic Cholecystectomy (6)

Criteria ---

Minimal Access invasive surgery

Less recovery period and time saving

Symptomatic cases of cholelithiasis with cholecystitis (9)

GB Calculi with sign of inflammation.

Early lap cholecystectomy within 24 hours as emergency case, in younger patients with mild to moderate classic RUQ pain with history of 2 or more attacks of pain, mild fever, without comorbidities

Less post-operative pain

Better cosmesis

No significant difference in cost between Laparoscopic cholecystectomy versus open cholecystectomy.

Late Laparoscopic Cholecystectomy --after 72 hours to 6 days --as selective case.

Complication --damage to Bile Duct

3. Open Cholecystectomy --- 76 (25.3 %)

Certain criteria that may require open cholecystectomy as follows -- (7)

Inflammation of Gall Bladder and Biliary tree

Inflammation of abdominal lining (Peritonitis)

Cholecystitis with cholelithiasis

Gall Stone Ileus

Patient with cardio-pulmonary Disease

Suspected mass in Gall Bladder with Calculi

GB Calculi with Trauma

Acute Cholecystitis with lithiasis

C T Scan abdomen is usually advised in complicated cases of acute calculous Cholecystitis, suspected cases of mass on GB area on ultrasound, in empyema of GB and to rule out pancreatitis /Hepatitis.

Demerits--

Needs long Hospital stay around 2 weeks

Recovery period more than lap cholecystectomy and to return to normalcy.

Complications --

Infection

Intra-operative / Post-operative Bleeding

Bile Leakage

Injury to Bile duct, Intestine, Blood vessels

Deep Vein Thrombosis

Risk from General Anaesthesia

Risk of Post Cholecystectomy syndrome --Upset Stomach, Nausea, and vomiting, Gas bloating, +/- loose motions, Persistent Pain in Right Upper Quadrant of Abdomen.

Dropped GB Calculi

Occult Choledocholithiasis

Stump Cholecystitis

Retained cystic Duct Stump

Incomplete or partial cholecystectomy

4. Conversion Surgery ---10 (3.3%)

This Method Is Required In Some Inevitable Conditions, Like Presence Of Gb Polyp, Presence Of Concomitant Disease And Adhesions Due To Past History Of Abdominal Surgery. (8)

Sometimes conversion have been indicated due to complications related to anesthesia , severe chronic cholecystitis with cholelithiasis , thermocoagulation and concomitant disease like Diabetes , Hematological disorders , cardiovascular and respiratory disease.

One of the main cause of conversion is due to bile Duct injury / Adhesions due to Fibrosis at Calot's triangle or intraoperative Hemorrhage ,rare causes koch's Abdomen and Malignancy .

5. Post-operative Follow Up __ Recent /Or Delayed

The Most Common Problem After Cholecystectomy Is Development Of Diarrhea In 5 To 8% Of Patients.

Few cases may have experience of recurrent pain in abdomen termed as Post Cholecystectomy syndrome.

Many patients with post cholecystectomy may develop long term functional pain.

Some of the patients may have problem of motility disorder of sphincter of oddi, termed as Biliary Dyskinesia where sphincter fails to relax normally following ingestion of meal.

Post-operative follow up ultrasound is required in each case to rule out above conditions before discharge from hospital.

RESULTS—

The mean operation time for laparoscopic cholecystectomy(45-65 min.) was significantly shorter as compared to open cholecystectomy (60-90 mts min) as shown in Table number 3 as follows :-

Table 3. Duration Of Operation Time

TYPE OF OPERATION	RANGE OF OPERATION TIME (MIN)	MEAN OPERATION TIME
LAP. CHOLE	50-80	65 MIN
OPEN CHOLE	60-120	90 MIN

Table 4. Complications Of Lap Chole. Versus Open Cholecystectomy

COMPLICATIONS	LAP. CHOLE	OPEN CHOLE
WOUND INFECTION	04	06
INTRA OPERATIVE BLEEDING	03	01
ABDOMINAL INFECTION	0	01
POST OP ILEAC	08	03
PANCREATITIS	0	0
BILE DUCT INJURY	01	0
CARDIAC PROBLEMS	01	0
DEATH	0	0
PNEUMONIA	02	0
SUBCUTANEOUS EMPHYSEMA	03	0
DEEP VEIN THROMBOSIS	0	01

It has been observed in our study that the time period of post-operative pain and analgesia significantly shorter in laparoscopic cholecystectomy group (1 to 3 days, mean 2 days) as compared to open cholecystectomy (3 to 8 days, mean 5.5 days).

The mean hospital stay was 2.4 days after laparoscopic Cholecystectomy and 4.8 days following open cholecystectomy.

As per our study, there was short hospital stay (2.4 days) in laparoscopic surgery as compared to open cholecystectomy (4.8 days) The conversion of laparoscopic to open cholecystectomy was reported in 10 cases out of 300 patients (3%) of selected cases of planned for laparoscopic cholecystectomy. Six cases were converted to open surgery due to marked adhesions, two cases for bile duct injury and two cases due to intra-operative hemorrhage (12).

The wound infections were higher in open cholecystectomy as compared to laparoscopic cholecystectomy. Post-operative ileus was seen in eight patients of open cholecystectomy so needed for continuation of nasogastric decompression .The post-operative pain

and use of analgesia was significantly less as compared to open cholecystectomy.

DISCUSSION –

In the modern era of surgery, laparoscopic cholecystectomy has become a modality of choice due to having many benefits over open cholecystectomy because of better technique with a small incision by using minimally access, reducing pain with early healing thereby short hospital stay with less morbidity and mortality.

The laparoscopic surgery was first performed by LYON, France in March 1987 by Philippe Mouret, a general surgeon having vast knowledge and experience in using laparoscope.

A meta-analysis study reveals high sensitivity and specificity of Abdominal Ultrasound in diagnosis of Gall Bladder Calculi were 84% and 99%.

The Diagnosis of Gall bladder Calculi is scarce in accuracy by Computer Tomography Scan.

There is minimal or No role of drugs in dissolution of Gall Bladder Calculi or ESWL or combination in setting of ACC.

The laparoscopic/ open cholecystectomy is method of choice for Acute Calculous Cholecystitis.

The delayed laparoscopic cholecystectomy is considered if performed between 7 days to 45 days after initial diagnosis while early laparoscopic cholecystectomy is usually performed with symptoms less than 72 hours but within 4 to 6 days of diagnosis (14).

The combination of detailed clinical history with clinical findings, laboratory tests and Ultrasound Abdomen by a competent radiologist is resulted in accurate diagnosis of Acute Calculous Cholecystitis. There has been a lot of debate whether to operate asymptomatic gall bladder calculi or not.

Truly speaking, Cholelithiasis is a benign disease because 70 to 86% of patients remain asymptomatic or have minor episodes of vague pain in abdomen.

Several studies have proved that incidentally detection rate of gall bladder calculi is more after ultrasonography which became investigation of choice and easily available in developing country like India.

The long duration follow up study reveals that gall stones remain symptoms free for a period of 20 years or more in majority of patients, only 15 to 20 % cases develop biliary colic.

There is an upsurge in number of cases of laparoscopic cholecystectomy because of easy availability of expert laparoscopic surgeons in almost all the major cities of India and increase detection rate of Gall Bladder calculi by ultrasound abdomen, resulting 50 to 60 % increase in number of cholecystectomies worldwide.(9)

The most important indications of asymptomatic gall stones laparoscopic surgery are presence of co morbidities like diabetes , hypertension , Multiple Big Sizes G B Calculi , and hemolytic anemia , The prophylactic laparoscopy cholecystectomy is also advocated in asymptomatic cholelithiasis at early age to prevent complications later in age like cholangitis, pancreatitis, choledocholithiasis and least chances of development of malignancy.

Open Cholecystectomy is a valid option for advanced inflammation, gangrenous Gall Bladder and main bile duct injury.

The dilated CBD is strong predictor of Calculous on ultrasound Abdomen imaging, especially associated with abnormal ALP, Bilirubin and ALT of patients >125 and further evaluated by ERCP/MRCP and EUS. .

Per cutaneous transhepatic Gall Bladder drainage (PT-GBD) is generally recognized as the preferred Technique in patient with Acute Calculous Cholecystitis.

Conversion rate in laparoscopic cholecystectomy has reduced

significantly due to availability of well trained expert surgeons. The bile duct injury rates have been markedly reduced

Table 5. Operative Time & Post – Op Hospital Stay (comparison)

VARIOUS SERIES	MEAN OF TIME OPE (MIN)/ POST OP HOS STAY DAYS	MEAN OF TIME LAP CHOLE MIN/ POST OP HOSPITAL STAY
CH.CHAU EAL	84.8 MIN /10.1 DAYS	92.2 MIN / 7.1 DAYS
LUJAN ET AL	77 MIN / 8.1 DAYS	88 MIN / 3.3 DAYS
GUPTA ET AL	41.89 MIN / 4 DAYS	66.28 MIN / 3 DAYS
KARIM ET AL	70 MIN / 5.46 DAYS	103.98 MIN / 3.7 DAYS
OUR STUDY	65 MIN / 4.8 DAYS	90 MIN / 2.4 DAYS

Now a days, the post- operative hospital stay time in laparoscopic cholecystectomy is markedly reduced for 48 hours in major big cities of India.

According to Girgin et al, Patient's age, Mannheim peritonitis index >29 and comorbidities are significantly related to morbidity and mortality & length of hospital stay.

Siddiqui et al in their study observed that frequency of wound infection is 4 times less in laparoscopic as compared to open cholecystectomy in acute cholecystitis cases.

CONCLUSION –

Now a days, Laparoscopic cholecystectomy is an efficient method of choice, particularly in case of acute cholecystitis, not only in India but Worldwide too.

There is a major role of imaging ,mainly ultrasound abdomen for early diagnosis , management (treatment) and follow up cases of gall bladder calculi (cholelithiasis) while C T scan/MRI Abdomen is indicated in complicated cases of gall bladder disease like empyema , polyp of G.B. and to rule out malignancy and other diseases like Pancreatitis , CBD Calculi / or mass , cholangitis and hepatic metastases .(10) Role of MRCP is advocated in CBD calculi and malignancy & anomalies of hepato-biliary system.

One of the main role of post- operative follow up ultrasound abdomen is to rule out any complications.

In spite of that, open Cholecystectomy is preferred method in remote areas by Surgeons those are not well trained in laparoscopic surgery and in difficult cases of cholecystectomy & in conversion cases.

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Data Collection from CMS office , Radiodiagnosis,Surgery (OT) and MOD .

Ethical approval and patient's informed consent -- taken in our Retrospective study ,because the patient's identities were not disclosed in any manner .

Consent for Publication --all the images is completely anonymised without disclosing patient's identity.

Competing Interests – The authors declare that they do not have any competing interests.

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METHODOLOGY:

Retrospective study, observational and performed at one tertiary hospital in G.S.Medical College and hospitals, Pilkhuwa, Distt .Hapur (U.P.), INDIA ,245304.

RISK FACTORS ---

Age more than 30 years , Gender –more in female than male , Family History ,Obesity , Rapid weight loss ,Hemolysis ,Raised serum lipids , Raised serum bilirubin , Cirrhosis , Stasis of biliary flow in G.B, certain Medications, Pregnancy and oral Contraceptives.

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