
**"A PROSPECTIVE STUDY TO EVALUATE USE
OF NEUTROPHIL TO LYMPHOCYTE RATIO
(NLR) AS A MARKER FOR SEVERE ACUTE
CHOLECYSTITIS"**

BY

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JAWAHARLAL NEHRU MEDICAL COLLEGE
BELAGAVI, KARNATAKA**

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KLE Academy of Higher Education and Research
Belagavi, Karnataka

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LIST OF ABBREVIATIONS

AC	:	Acute Cholecystitis
NLR	:	Neutrophil Lymphocyte Ratio
HDL	:	High Density Lipoprotein
CRP	:	C – Reactive Protein
CT	:	Computed Tomography
MRI	:	Magnetic Resonance Imaging
USG	:	Ultrasonography
ICU	:	Intensive Care Unit
WBC	:	White Blood Cells
RUQ	:	Right Upper Quadrant
AST	:	Aspartate aminotransferase
ALT	:	Alanine transaminase
BMI	:	Body Mass Index
KLE	:	Karnataka Lingayat Education
KAHER	:	KLE Academy of Higher Education and Research
OPD	:	Outpatient Department

ABSTRACT

BACKGROUND:

Acute cholecystitis is one of the most common afflictions of the gastrointestinal system presenting to OPD or emergency department. Reported incidence of cholelithiasis is 10% to 15%. Annually, symptom development in asymptomatic people ranges from 1% to 2%. Delayed identification of acute cholecystitis can lead to complications (hemorrhage, empyema, gangrene, perforation of gallbladder, emphysema, adhesions, challenging dissection) thus leading to increased morbidity. Overall reported mortality is 1%.

A new, inexpensive and simple predictor of severe acute Cholecystitis is needed for stratification of patients for urgent biliary drainage, close monitoring, and intensive care unit (ICU) care. Thus, Neutrophil Lymphocyte ratio is being proposed as a potential prognostic biomarker for prediction of severe acute cholecystitis.

AIMS, OBJECTIVES:

1. To evaluate the utility of the Neutrophil Lymphocyte Ratio as a prognostic indicator in patients with acute cholecystitis, and to identify a relevant ratio value that discriminates between mild, moderate and severe acute cholecystitis.
2. To evaluate and compare the discriminative powers of the neutrophil-to-lymphocyte ratio with White Cell Counts, CRP and radiological modalities (USG or CT) in diagnosing severe acute cholecystitis with help of Tokyo guidelines.

METHODS:

This was a prospective observational study conducted in KLE'S Dr. Prabhakar Kore Medical College and MRC, Belagavi for a duration of 1 year. Demographic data , clinical characteristics, investigations and management of total 110 patients who were more than 18 years presenting with acute cholecystitis were collected at the time of their initial visit to outpatient department / emergency department. NLR was calculated at time of admission as the absolute neutrophil count divided by the absolute lymphocyte count. An abdominal CT / USG was performed within 6 hours of arrival. Patients were categorised into mild, moderate or severe acute cholecystitis group based on Tokyo guidelines.

RESULTS:

Out of 110 patients, 64 were male and 46 were female. 23.64% had severe acute cholecystitis, 30.91% had moderate and 45.45% had mild acute cholecystitis based on Tokyo guidelines classification. Mean hospital stay and ICU stay was more in severe cholecystitis group. Diabetes mellitus was common associated comorbidity in severe cholecystitis (35.48%). NLR differentiates severe cholecystitis from nonsevere cholecystitis with sensitivity of 97% and specificity of 88% as per our study. Gallbladder perforation was most common secondary complication followed by empyema, gangrenous and emphysematous changes respectively. As per study, NLR ranges <6.5 in mild, 6.5 to 10 in moderate and >10 in severe acute cholecystitis. Gallbladder wall thickness, pericholecystic collection and fat stranding were radiological changes associated with severe cholecystitis.

CONCLUSION:

NLR has proved to be a prognostic marker to determine severity, course of disease in patients with acute cholecystitis which will help in appropriate management and better patient outcome.

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INTRODUCTION

Acute cholecystitis is one of the common afflictions of the gastrointestinal system which presents to the emergency department for hospital admission and surgical management¹. Acute cholecystitis is defined as inflammation of the gall bladder occurring due to cystic duct obstruction from stones, sludge leading to bile stasis and subsequent mechanical, chemical or infectious irritation of the gall bladder wall². 90% cases constituted are because of cystic duct blockage by single or multiple gallstones¹.

The incidence of cholelithiasis varies from 10% to 15% as it is governed by the age, race, genetic predisposition, gender, nutritional status, and the presence of certain conditions like hemolytic anemia, cirrhosis, pregnancy, non High Density Lipoprotein(HDL) hyperlipidemia, Crohn's disease etc. The majority of gall stones (90%) are formed by crystallization and precipitation of excess biliary cholesterol from endogenous or dietary lipids. 80% of these patients remain asymptomatic. Annually, symptom development in asymptomatic people ranges from 1% to 2%. Patients without biliary symptoms are typically discovered to have gall stones during abdominal radiological investigations or at the time of surgery for unrelated diagnosis. Once symptomatic, they will have recurrent bouts of biliary colic^{3,11}.

Increased morbidity results from delayed identification and treatment of acute cholecystitis because it progresses to severe cholecystitis, such as hemorrhage, empyema, gangrene, perforation of gallbladder, adhesions, challenging dissection of Calot's triangle, emphysema or when the pathological examination indicated xanthogranulomatous cholecystitis³. The overall mortality of 1% is reported in

patients with acute cholecystitis. However, in the older age group and patients with associated comorbidities, mortality increases to 2%-3%⁴.

As per Tokyo guidelines from 2007, updated in 2013 and 2018, acute cholecystitis is defined by right upper quadrant pain, guarding, fever, Murphy's sign, elevated leucocyte count and C-reactive protein (CRP)⁴. It is challenging to diagnose severe cholecystitis both clinically and radiologically. Patients with uncomplicated acute cholecystitis and those with severe acute cholecystitis have significantly different morbidity and death rates⁷. Therefore, it is essential to properly diagnose and treat patients who are at risk of developing severe cholecystitis in order to avoid any related consequences.

Literature shows that ultrasound is more sensitive than CT for detecting cholelithiasis, but CT is more sensitive than ultrasound for diagnosing complications of acute cholecystitis. CT is particularly useful in patients without the typical clinical signs or symptoms⁴. MRI can be used when biliary tree anatomy has to be delineated.

The neutrophil lymphocyte ratio (NLR), a straightforward, economical formula that employs information from a typical full blood count and is calculated using the ratios of circulating neutrophil and lymphocyte numbers. The secretion of platelet-activating factors and arachidonic acid metabolites due to the inflammatory process leads to neutrophilia. Simultaneously relative lymphopenia results due to cortisol-induced stress. Thus NLR correctly shows the ongoing inflammatory process in the body. By prioritizing treating the sickest of patients first, proper perioperative management can be enabled thus giving a good medical or surgical outcome.

There is a need for a new, inexpensive, and simple predictors of severe acute cholecystitis, to stratify patients for urgent biliary drainage, close monitoring, and selective transfer to the intensive care unit (ICU) as early as possible and NLR is being tested for same. In patients in whom the CT reporting is not confirmatory, NLR could be used to prioritize surgery if there is a risk of cholecystitis worsening from mild to severe. Severity grading plays a vital role in predicting disease prognosis , the length of hospitalization and the laparotomy conversion rate.

OBJECTIVES

1. To determine the usefulness of the Neutrophil to Lymphocyte ratio as a prognostic marker in acute cholecystitis patients and to find out a suitable value that distinguishes between mild, moderate, and severe acute cholecystitis.
2. To evaluate and compare the use of the neutrophil-to-lymphocyte ratio (NLR) with White Cell counts, CRP and radiological modalities (USG or CT) in diagnosing severe acute cholecystitis with help of Tokyo guidelines.

REVIEW OF LITERATURE

A. EMBRYOLOGY

In the primitive midgut's ventral wall an outpouching develops during the fourth week of intrauterine life.

1. **3-mm stage :** Cranial bud which blossoms into liver lobes. The gallbladder and extrahepatic biliary system develops from caudal bud. By day 26 of development, the cystic diverticulum develops from caudal duct which forms the gall bladder and cystic duct by the end of 4 weeks.
2. **5mm stage :** Common hepatic duct is formed from part of pars hepatica distal to the origin of pars cystica and common bile duct is formed from a part between pars cystica and duodenal part of foregut.
3. **7mm stage :** Formation of the liver, hepatic ducts, gallbladder, cystic duct and ventral pancreas
4. **12-mm stage:** Ventral pancreatic bud has rotated 180degrees clockwise around the duodenum causing fusion of the ventral and dorsal buds to form the complete pancreas by the sixth or seventh week of gestation.

The liver starts to secrete bile at the twelfth week of intrauterine life⁷.

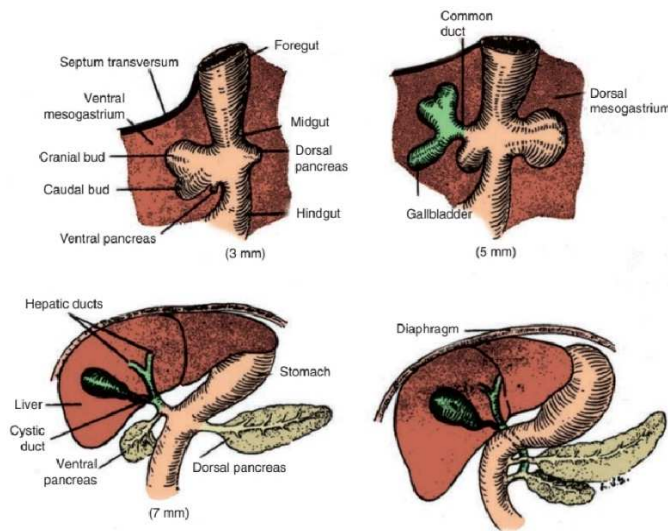


FIGURE 1: EMBRYOLOGICAL DEVELOPMENT OF EXTRAHEPATIC BILIARY TREE

B. SURGICAL ANATOMY:

1. GALL BLADDER

- 7 to 10cm long, pear shaped sac located in anatomic fossa on the inferior surface of liver.
- Average capacity is 30 to 50ml (Maximum 300ml in cases of outflow obstruction)⁸

Gall bladder is anatomically divided into 4 parts –

- Fundus:** Round in shape with a blind end exceeding 2 cm below inferior margin of liver
- Body:** Composed of elastic tissue which helps in distension.
- Infundibulum:** It is a mucosal outpouching present at junction of cystic duct and neck
- Neck:** It lies in deepest part of gall bladder fossa connecting to cystic duct.

Peritoneal lining of liver extends to cover fundus and inferior surface of gall bladder.⁹

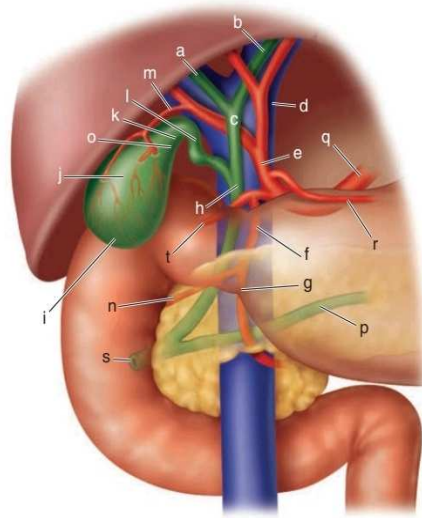


FIGURE 2: BILIARY ANATOMY :

- A. Right hepatic Artery
- B. left Hepatic Duct
- C. Common hepatic duct
- D. Portal vein
- E. Hepatic artery Proper
- F. Gastroduodenal artery
- G. Right gastroepiploic artery
- H. Common bile duct
- I. Fundus of gallbladder
- J. Body of gallbladder
- K. Infundibulum of gallbladder
- L. Cystic duct
- M. Cystic artery
- N. Superior pancreaticoduodenal artery
- O. Neck of GB
- P. Pancreatic duct
- Q. Common hepatic artery
- R. Right gastric artery
- S. Ampulla of Vater
- T. Supraduodenal artery

2. EXTRAHEPATIC BILIARY TREE

- a. **Hepatic ducts** : Left hepatic duct is longer than right and it is more likely to be dilated in case of distal obstruction.
- b. **Common hepatic duct** : Common hepatic duct is formed by confluence of right and left hepatic duct close to the liver surface. Length=1 to 4 cm, diameter 4mm. Lies to right of hepatic artery and anterior to portal vein.
- c. **Cystic duct** : It exits from gall bladder. Has variable length and course. It has spirally arranged folds in mucosa known as valves of Heister.
- d. **Common bile duct** : Cystic duct joins common hepatic duct at acute angle to form common bile duct. 7 to 11cm long, 5 to 10mm diameter.

4 parts =

1. **Supraduodenal:** Length = 2.5cm; found on the right side of the hepatic artery and along the free margin of the lesser omentum, anterior to the portal vein.
2. **Retroduodenal** segment lies posterior to 1st part of duodenum moving away from portal vein and hepatic artery.
3. **Infraduodenal** segment is on posterior surface of pancreatic head & traverses through it.
4. **Intraduodenal** segment joins with pancreatic duct and ends by opening to ampulla of Vater in 2nd part of duodenum⁹.

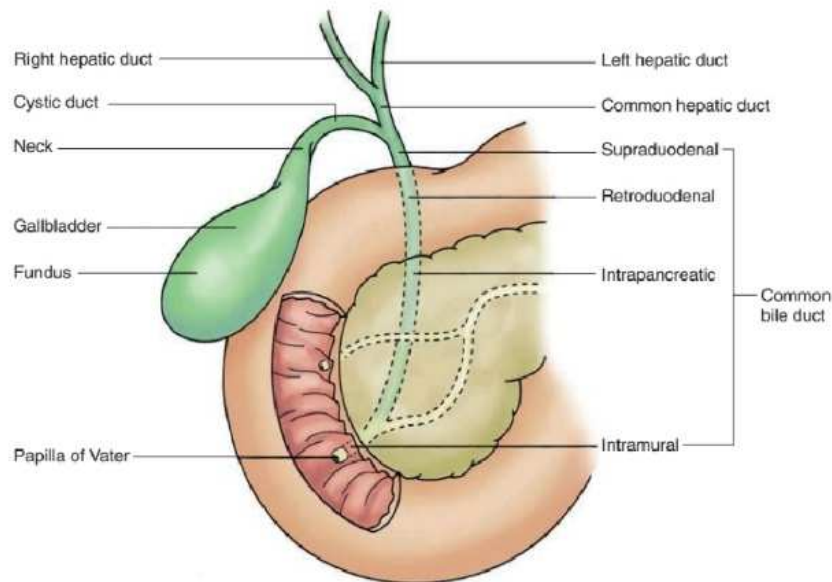


FIGURE 3 : ANATOMICAL DIVISION OF BILIARY SYSTEM

SPHINCTER OF ODDI

It is 4-6 mm in length and its motility is controlled by interstitial cells of Cajal^{8,9}. It is a muscle coat made of thick circular muscle fibres, which surrounds common bile duct at ampulla of Vater . Functions :

1. It prevents regurgitation of duodenal contents into biliary tree.
2. Regulates the flow of pancreatic and biliary juice
3. Diverts bile to gall bladder in fasting state.

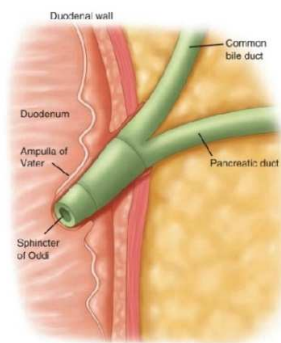


FIGURE 4 : SPHINCTER OF ODDI

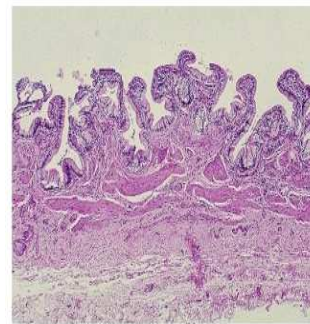


FIGURE 5 : GALL BLADDER HISTOLOGY

3. HISTOLOGY OF GALL BLADDER:

- a. Mucosa : Single layer of Simple columnar epithelium containing fat globules , cholesterol . Tubuloalveolar glands found in mucosal lining of neck and infundibulum secrete mucus.
- b. Lamina propria
- c. Muscular layer : ill defined circular , longitudinal and oblique muscle fibres
- d. Adventitia : Contains connective tissue, vessels , lymphatics , nerves
- e. Serosa¹⁰

4. BLOOD SUPPLY

A. ARTERIAL SUPPLY :

- Cystic artery has a variable origin which is most commonly arising as a branch from right hepatic artery supplying major area of gall bladder (lies in close proximity to cystic duct in Calot's triangle). Its superficial and deep branches given at neck of gall bladder anastomose over the body and fundus of gallbladder. As cystic artery forms an end artery, its occlusion leads to gangrene of the gall bladder⁹.
- Caterpillar turn / Moynihan's hump: dangerous anomaly comprising of short cystic artery and tortuous right hepatic artery which can lead to inadvertent arterial injury or bleeding during cholecystectomy⁹.

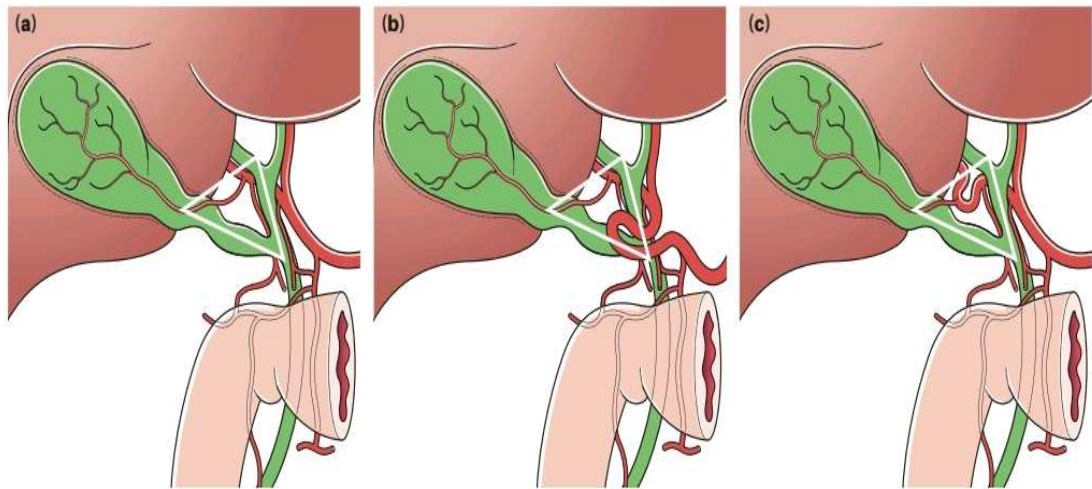


FIGURE 6 : A. CALOT'S TRIANGLE B. TORTUOUS RIGHT HEPATIC ARTERY WITH SHORT CYSTIC ARTERY ; B AND C ARE EXAMPLES OF MOYNIHAN'S HUMP.

B. VENOUS DRAINAGE:

Veins draining the bile ducts drain into 9 o'clock & 3 o'clock veins along common biliary channel. The venous supply of gallbladder is different since multiple smaller veins directly pass into tributaries of the right portal vein within the liver, straight from the gall bladder through its bed¹⁰.

5. LYMPHATICS :

Cystic lymph node of Lund which lies in the angle at the junction of the cystic and common hepatic ducts drains the gall bladder. The efferent vessels then drain into the liver at its hilum and subsequently into the coeliac lymph nodes. The subcapsular lymphatic vessels of the liver merge with the subserosal lymph vessels of the gallbladder¹⁰.

6. ANATOMICAL VARIATIONS : Anatomical Anomalies in the formation of extrahepatic biliary system and gall bladder are vital to be known to prevent grave outcome during cholecystectomy⁹.

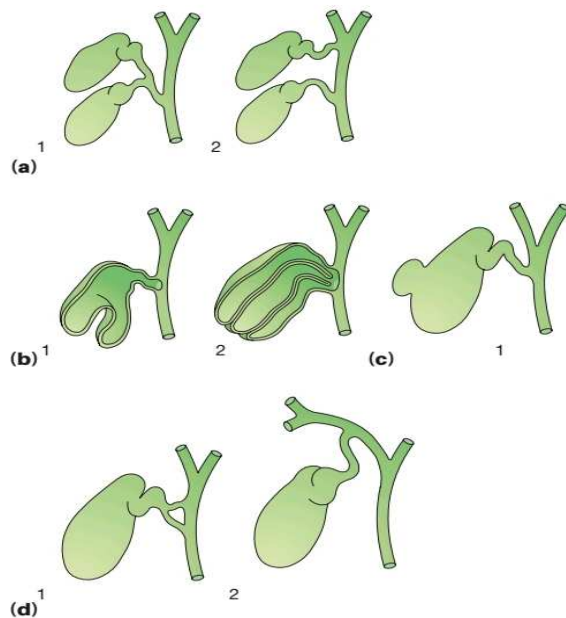


FIGURE 7 : MAIN VARIATIONS IN GALLBLADDER AND CYSTIC DUCT ANATOMY :

- a. Double gall bladder
- b. Septum of gallbladder
1. Phrygian cap
- c. Diverticulum of gallbladder
- d. Variation in cystic duct insertion

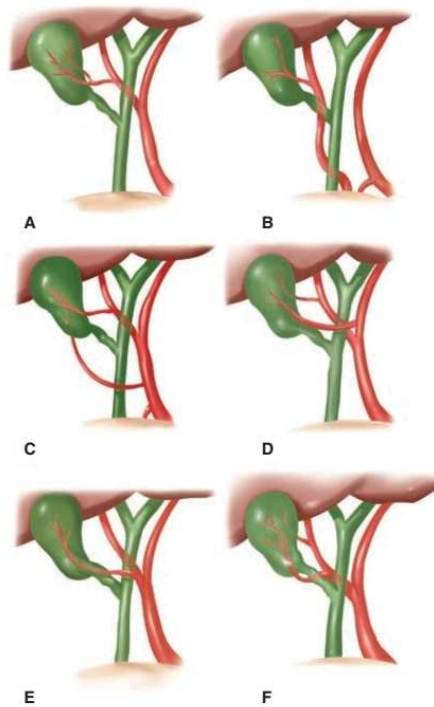


FIGURE 8: VARIATIONS IN CYSTIC ARTERY

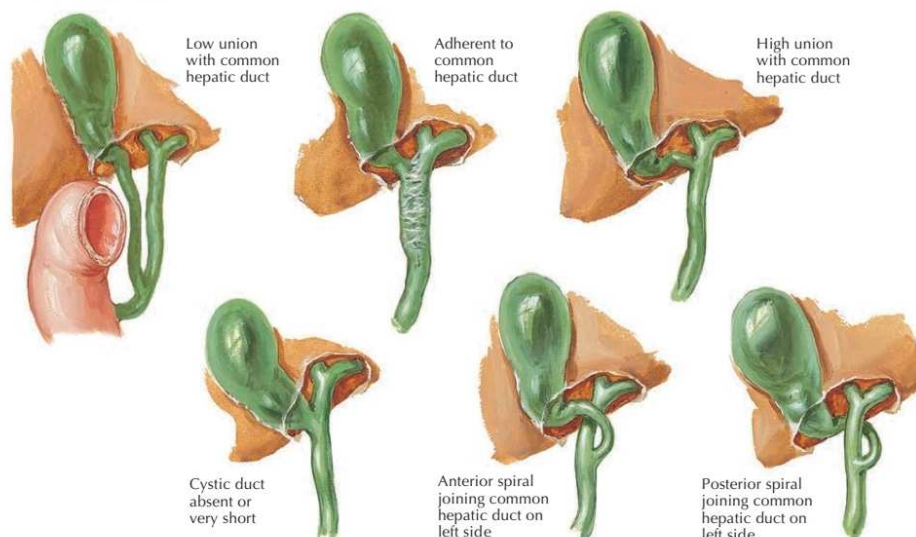


FIGURE 9: VARIATIONS IN CYSTIC DUCT

7. NERVE SUPPLY

1. Parasympathetic nerve supply from Anterior Vagal trunk.
2. Sympathetic nerve supply (T7-9 cell bodies) from celiac ganglion .
3. Right infrascapular referred pain is due to the right sympathetic fibres, which is the main afferent pain fibres passing over the T7-9 spinal segment. Some afferent fibres from the right phrenic nerve go across the hepatic, phrenic, celiac plexuses near gallbladder causing right hypochondrial referred pain, radiating to back between the shoulder blades in gallstones.
4. The contraction of gallbladder & ampullary sphincter relaxation is governed by parasympathetic system and inhibition of contractions of gallbladder by sympathetic system^{9,10}.

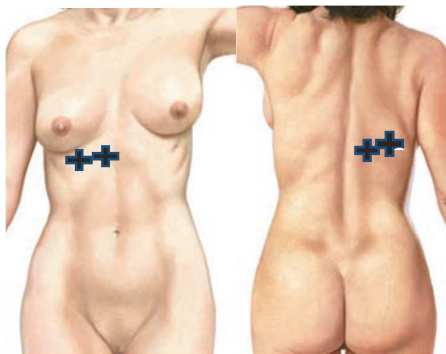


FIGURE 10 : DISTRIBUTION OF PAIN

8. CALOT'S TRIANGLE :

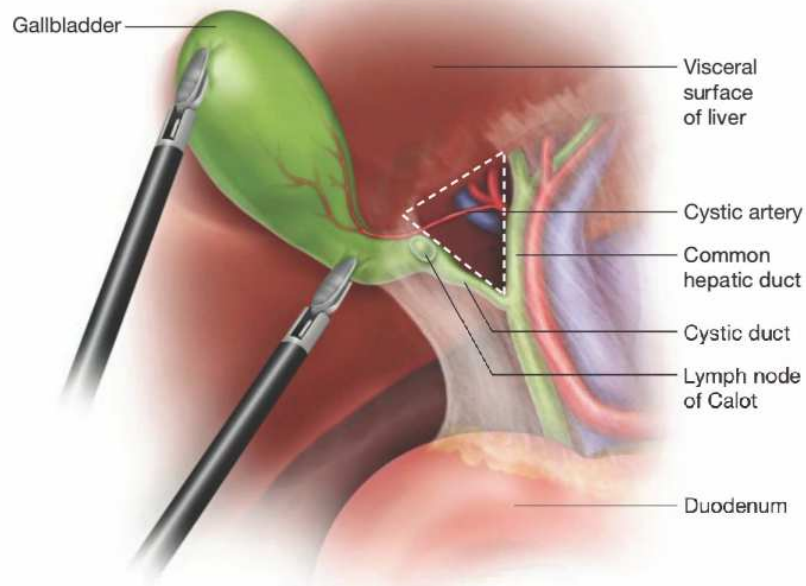


FIGURE 11 : CALOT'S TRIANGLE

BOUNDARIES:

Above : segment V of inferior border of liver

Medially: common hepatic duct

Laterally: cystic duct and the neck of gall bladder

CALOT'S TRIANGLE CONTENTS

- 1) Right hepatic artery
- 2) Cystic artery
- 3) Cystic lymph node of Lund
- 4) Small cystic veins
- 5) Autonomic nerves piecing gall bladder
- 6) Adipose tissue
- 7) Some accessory ducts draining GB.

9. LAPAROSCOPIC ANATOMY OF GALL BLADDER

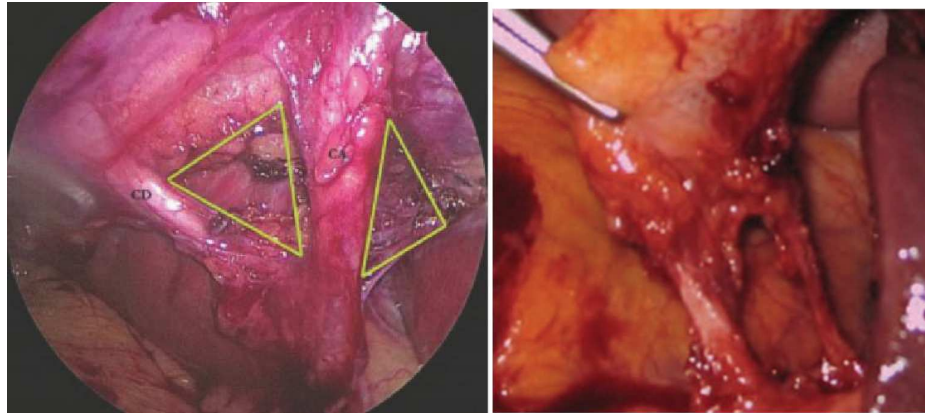


FIGURE 12(A) : Critical view of safety in laparoscopic cholecystectomy
FIGURE 12 (B) The critical view in open cholecystectomy.

Laparoscopic first view→ Demonstration of subphrenic space, abdominal side of the diaphragm and diaphragmatic surface of the liver. Gall bladder fundus is seen in the inferior liver surface. The left and the right sub phrenic spaces are separated by falciform ligament.

Rouviere's sulcus→ It is a sulcus/ fissure between the right and caudate lobe of liver that is clearly seen in most of the individuals. This is present where the right pedicle enters liver at the level of porta hepatis. The dissection has to be carried out above the level of this sulcus to prevent bile duct injuries.

Critical view of safety→ Important aspect of laparoscopic anatomy of gall bladder, essential to prevent bile duct injury. Calot's triangle dissection is most vital step of laparoscopy. Strasberg et al described this technique of Critical view which includes the dissection of all tissue at the triangle of Calot except the cystic duct and cystic artery with the base of liver bed being exposed. The dissection should be such that only two structures are seen entering the gallbladder which can only be the cystic duct and artery¹¹.

C. PHYSIOLOGY OF GALL BLADDER =

In a normal adult, around 500 to 1000ml of bile is secreted from liver per day in response to neurogenic, humoral and chemical stimuli. Gall bladder acts a reservoir of bile before it is spontaneously released into the duodenum intermittently. The flow of bile into duodenum is controlled by Sphincter of oddi⁸.

The sphincter contracts during a fast to produce a pressure differential between the bile duct and gall bladder, which causes the gall bladder to fill. After consumption of meal, a well coordinated relaxation and contraction of sphincter of Oddi empties the bile into duodenum. In reaction to low pH and food consumption, mucosa of duodenum secretes cholecystokinin which controls the sphincter actions by acting on smooth muscle fibres of gall bladder. Normally, 95% of bile is absorbed into terminal ileum through enterohepatic circulation^{8,9}.

Functions of gallbladder:

1. Storage organ for bile (80% bile produced by liver, during fasting)
2. Concentration of the hepatic bile 5-10 times by absorption of bicarbonate, water, sodium chloride
3. Secretes mucus for mucosal protection
4. Maintains the pressure within the biliary tree

Water is absorbed both passively and actively by gall bladder hence biliary concentration in liver and gall bladder varies. Gall bladder readily absorbs calcium and magnesium.

Gallbladder bile is acidic as compared to basic hepatic bile due to absorption of chloride, bicarbonate and hydrogen ions⁹.

TABLE 1 : BILE COMPOSITION

Characteristics*	Hepatic Bile	Gallbladder Bile
Na	160	270
K	5	10
Cl	90	15
HCO ₃	45	10
Ca	4	25
Mg	2	4
Bilirubin	1.5	15
Protein	150	200
Bile acids	50	150
Phospholipids	8	40
Cholesterol	4	18
Total solids	—	125
pH	7.8	7.2

*All determinations are milliequivalents per liter; except for pH. Significant ranges of all elements may occur.

BILE ACIDS AND SALTS

Bile acids : 500 to 600 mg in a day

1. Primary - cholate / chenodeoxycholate
2. Secondary - deoxycholate / lithocholate
3. Tertiary –ursodeoxycholate

They are synthesized in liver from cholesterol. They help in the digestion and absorption of fat from gut by conjugating with glycine and taurine to act as anions .

Terminal ileum absorbs conjugated bile acids which accounts to 80%. Bacteria in colon will deconjugate rest of the bile and forms secondary bile acids. 95% bile acids enter enterohepatic circulation.

BILE PIGMENTS

The major bile pigment bilirubin is formed from breakdown of old RBCs by the reticuloendothelial system. Biliverdin is produced from bilirubin.

BILIRUBIN METABOLISM AND EXCRETION

Haemoglobin breakdown forms bilirubin.

Albumin binds to the bilirubin in circulation. Hepatocytes absorb free bilirubin by binding it to cytoplasmic proteins. Bilirubin is conjugated by UDP – glucuronyl transferase into glucuronic acid. This acid forms bilirubin diglucuronide, a water soluble compound. Most of the bilirubin diglucuronide is transported into bile canaliculi actively against gradient and rest is disposed off in urine.

ENTEROHEPATIC CIRCULATION:

6 to 8 times / day.

The secreted bile salts drain into the canaliculi from the hepatocytes and further into the small bile ducts. They contain sodium and potassium salts which conjugate with glycine and taurine, forming primary bile salts. Secondary bile salts are formed in intestine due to alteration by bacterial gut flora, forming deoxycholate and lithocolate. They help in lipid solubility by formation of micelles hence facilitating its absorption. The bile salt pool is maintained mainly by gall bladder, followed by liver and small intestine.

Small intestine helps in absorption of 90 to 95 % of bile salts through either nonionic diffusion or mostly by sodium bile salt co-transport containing Na⁺K⁺ATPase present in terminal ileum. Resynthesis also happens from liver for the

amount lost in stools. 0.2 to 0.4 g in a day is the normal bile salt synthesis rate. About total of 3.5 g gets repeatedly recycled through the enterohepatic circulation.

D. NATURAL COURSE OF GALL STONE DISEASE

The prevalence of gall stones is known to be high but only few patients develop symptoms in course of their life and rest remain asymptomatic. The common presentation is postprandial right upper abdominal pain resulting from calculus in cystic duct. Gall stones may further cause complications like acute cholecystitis , choledocholithiasis ,gall stone pancreatitis, cholangitis, gallstone ileus , gall bladder carcinoma. Various studies have examined the likelihood of developing symptoms after incidental diagnosis of gall stone disease for unrelated condition. 80% of patients stay symptom free and about 2 to 3% become symptomatic every year. 3 to 5% of symptomatic patients are known to develop complicated gall stone disease. Perforation is common in the fundus of the gallbladder; it is least vascular. White bile occurs when the cystic duct is impacted with gallstones obstructing the flow of bile. Impaction of gallstones commonly occurs in Hartman's pouch⁹.

1. EPIDEMIOLOGY

Prevalence = 6-20% among Indian adults

Multifactorial risk factors.

1. Female sex and pregnancy = 3-fold increased risk due to excess cholesterol secretion due to increased oestrogen levels and gall bladder emptying is delayed by progesterone.
2. Age = Formation of calculi increases with aging

3. Obesity = Contractility of gall bladder is decreased due to bile supersaturated with cholesterol leading to a calculus formation
4. Rapid weight loss = Restriction of calories with excess mucin release leads to hepatic cholesterol production which results in sludge formation.
5. Drugs = Oral contraceptive pills, oestrogens , cephalosporins (3rd generation) , thiazides , octreotide known to increase the risk.
6. Systemic illnesses = Resistance to insulin is associated with Hypercholesterolemia which is seen in diabetes. Liver cirrhosis causes reduced secretion of bile salts and chronic hemolysis forming pigmented stones.
7. Gastrointestinal conditions like Crohn's disease / terminal ileal resection causes defective absorption of bile salts causing supersaturated bile.
8. Haematological conditions= Haemolytic anaemia , sickle cell disease , thalassemia , hereditary spherocytosis have increased propensity to form pigmented stones.

2. FORMATION OF GALL STONES

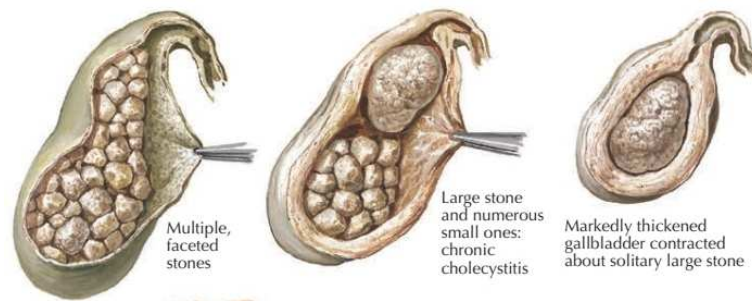


FIGURE 13 : GALL STONES

Multifactorial causes are known. Stone formation is known to occur due to imbalances between bile acids and concentrations of cholesterol in bile.

Supersaturated bile : Cholesterol is insoluble in water. Phospholipids hold cholesterol in a micelle which is stable thermodynamically. Supersaturation of bile occurs if there is decreased secretion of bile acids / lecithin with excess cholesterol forming cholesterol calculi.

Cholesterol nucleation : In bile which is cholesterol saturated , stones are formed from unilamellar phospholipid vesicles after cholesterol nucleation. Glycoprotein and mucin are known to help the nucleation process. Beta glucuronidase in bacteria such as E.coli lyses bilirubin glucuronide and forms insoluble deconjugated bilirubin . This complex then binds with calcium and forms stones in biliary tree⁸.

Impaired function of gall bladder : In presence of stones in biliary tree , gall bladder emptying is delayed leading to stasis. Absorption of calcium and secretion of glycoproteins and mucin by mucosa interferes with contractility and emptying of GB.

Enterohepatic circulation of bile acids : Fecal colonic flora , resection of ileum , deoxycholate and use of cholestyramine affects bile acid absorption.

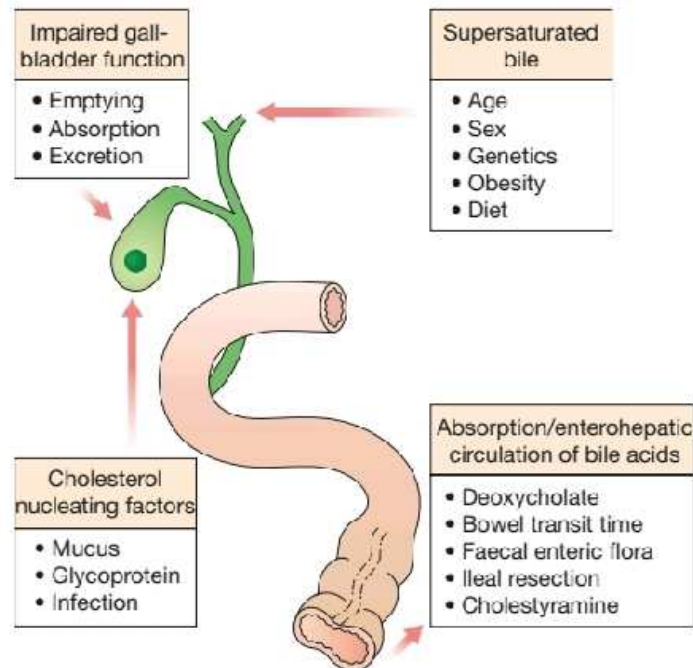


FIGURE 14 : FACTORS ASSOCIATED WITH GALLSTONE FORMATION

3. TYPES OF GALL STONES

1. Cholesterol stones =

- Stones purely formed from Cholesterol are rare.
- Smooth surfaced single large stone
- Pale yellow color
- Most are mixed containing >70% cholesterol , calcium , bile pigments
- Majority are radiolucent

2. Pigment stones =

- Black and brown (contain <20% cholesterol)
- Black stones : color is attributed to calcium bilirubinate complex with calcium phosphate and calcium bicarbonate , tiny, brittle , Spiculated .

seen in Hemolysis , liver cirrhosis , hereditary spherocytosis , sickle cell disease

- Brown stones :

Semisolid , tiny , Found in CBD , rarely in GB.

Calcium bilirubinate , calcium palmitate , calcium stearate and cholesterol.

Can be associated with parasites like clonorchis sinensis ,Ascaris lumbricoides.

3. **Mixed stones** =

- Multiple
- Faceted surface
- Pure central core and outer layer made from mixture of constituents
- Color depends on constituents
- Inflammatory origin of stones can be known by epithelial debris and bacteria present in laminated central nucleus.

E. ACUTE CHOLECYSTITIS :

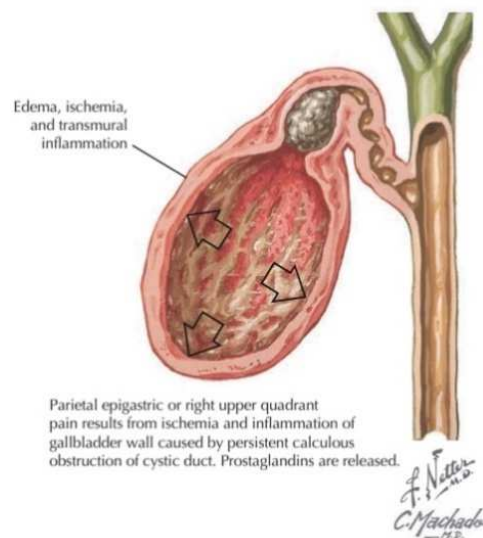


FIGURE 15 : PATHOPHYSIOLOGY OF ACUTE CHOLECYSTITIS

It is infection of gall bladder which is associated with gall stones in 90 to 95% cases.

Following obstruction of cystic duct by gallstone → gallbladder distension , inflammation and then gallbladder wall edema.

Secondary bacterial infection can occur in 15 to 20% patients.

In acute episode of cholecystitis , wall of gallbladder becomes grossly thickened , subserosal hemorrhages , hyperemic mucosa then necrosis¹¹.

CLINICAL FEATURES:

Symptoms:

1. It often begins as an attack of biliary colic with relapsing and remitting pain in right upper abdominal quadrant or epigastrium and radiating to back or interscapular area. Flatulent dyspepsia after fatty meal
2. Food intolerance to fatty foods
3. Nausea / vomiting
4. Fever
5. Jaundice if present is suggestive of biliary obstruction
6. Rarely , enteric obstruction due to gall stone ileus^{8,9}.

PHYSICAL SIGNS

1. Tenderness in right hypochondrium due to inflamed parietal peritoneum. It may or may not be associated with rigidity or guarding
2. Murphy's sign : Inspiratory arrest on deep palpation felt in right hypochondrium.
3. Palpable gallbladder in cases of mucocoele , emphysema , omentum covering inflamed gallbladder .

ACUTE CHOLECYSTITIS COMPLICATIONS

1. MUCOCELE

Once the inflammation settles down without resolution of obstruction, gallbladder mucosa secretes mucin and absorbs bile salts and pigments forming a mucocele.

2. EMPYEMA GALL BLADDER

Secondary bacterial infection of gall bladder following prolonged stone impaction causes formation of empyema or pus in gallbladder

3. PERFORATION OF GALL BLADDER WALL

Secondary bacterial infection leads to acute gangrenous cholecystitis which is prone for perforation. It can lead to frank bile peritonitis or may form a localized subhepatic abscess. Patient will present with toxic symptoms and will require emergency surgery. A chronic perforation into colon or duodenum will form cholecystoenteric fistula.

4. EMPHYSEMATOUS CHOLECYSTITIS :

If gas forming organisms like clostridium cause infection of gall bladder then gas can be seen in imaging studies .

INVESTIGATIONS

BLOOD TESTS :

1. Mild to moderate leucocytosis (12000 to 15000cells/mm³) is seen in acute cholecystitis. In severe cases ,>20,000cells/mm³ can be seen. A normal WBC count will not rule out acute cholecystitis.
2. In uncomplicated acute cholecystitis , liver and renal function tests will be normal.

In a few cases , mild elevation of serum bilirubin(<4mg/ml) with mild elevation of alkaline phosphatase , transaminases can be seen.
3. PT/ INR raise usually seen in case of liver dysfunction.
4. Neutrophil Lymphocyte Ratio : Neutrophil lymphocyte ratio has been found to be a prognostic marker for various inflammatory , infectious , malignant conditions. It is a indicator demonstrating systemic response of the body. (Details mentioned in further chapter)

RADIOLOGICAL INVESTIGATIONS

1. **Xray Abdomen plain :**
 - 10% radiopaque gallstones can be detected⁸.
 - Mercedes Benz / seagull sign = It is triradiate or biradiate shaped - radiolucent gas present at the center of stone.



FIGURE 16: PLAIN RADIOGRAPH SHOWING RADIOOPAQUE STONES

2. Ultrasound Abdomen

- Initial investigation of choice.
- The specificity and sensitivity for detection of GB stones is >90% and 70% respectively⁹
- Size , thickness of wall, polyps , number of stones , pericholecystic collection, size of CBD, intrahepatic biliary radical dilatations and sometimes calculi in CBD can be demonstrated.
- USG can detect acoustic shadowing by transducer due to the sound waves that are reflected by the calculi as small as 1mm size. Overdistended gallbladder with thin walls can be a mucocoele.
- Advantages : low cost, no radiation exposure and better anatomy of biliary system is delineated and can be performed on bedridden patients.
- Sonographic Murphy's sign : Probe tenderness in right hypochondrium over the gall bladder.

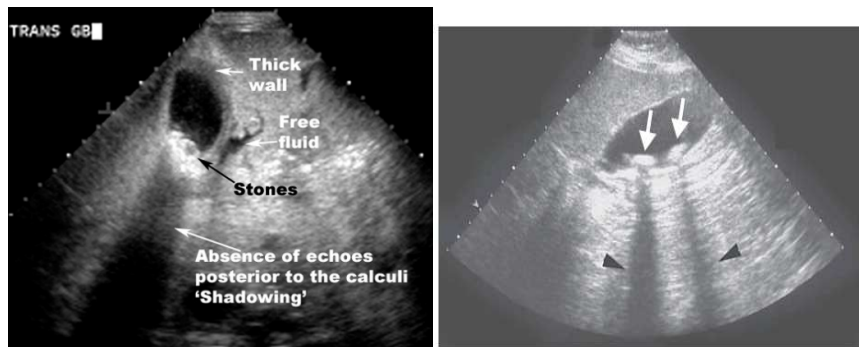


FIGURE 17 : ULTRASONOGRAPHY ABDOMEN : ACUTE CHOLECYSTITIS A AND B :White arrow - Stones within gallbladder ;Black arrow – Acoustic shadows from stone

Cholescintigraphy :

- It gives functional and anatomical information of liver, bile ducts, duodenum and gallbladder.
- ^{99m}Techetium-labeled derivatives of dimethyl iminodiacetic acid (HIDA, IODIDA) is given through veins.
- Uptake by Kupffer cells & then elimination in bile.
- Uptake by hepatocytes is visualized usually within 10 minutes of injection.
- In 90% of cases biliary tree and gall bladder can be seen within 30 minutes and bowel within an hour. Nonvisualization of gallbladder suggests acute cholecystitis. Lack of filling of gallbladder 4 hours after injection indicates cystic duct obstruction in suspected cases of acute cholecystitis, confirms diagnosis with sensitivity of 90%^{8,9}.

Computed tomography

- Inferior to ultrasonography in detecting gallstones. It is used as a screening study only.
- However it is preferred modality in detecting complicated cholecystitis. CT is initial investigation if gall bladder carcinoma is suspected.



FIGURE 18 : CT SCAN : GALL STONE WITHIN GALL BLADDER

Magnetic resonance cholangiopancreatography (MRCP)

- Non invasive and provide accurate high definition images demonstrating biliary pathologies like stricture, intraductal pathologies , obstruction and pancreatic diseases.

Endoscopic Retrograde Cholangiopancreatography (ERCP) :

- Diagnostic and therapeutic
- Procedure : Through ampulla of Vater, common bile duct is cannulated with a side viewing endoscope. Accurate bile duct images are obtained after injecting a water-soluble contrast into it and identifies the cause and level of obstruction in obstructive jaundice.
- Therapeutic techniques like sphincterotomy, stenting or stones can be extracted to relieve the obstruction. Bile aspirates or endoluminal brushings can be sent for cytological studies.
- Complications like pancreatitis and cholangitis can occur in 5% of patients after diagnostic ERCP and bile duct injury/ rupture and minimal bleeding can occur after sphincterotomy / lithotripsy⁹.

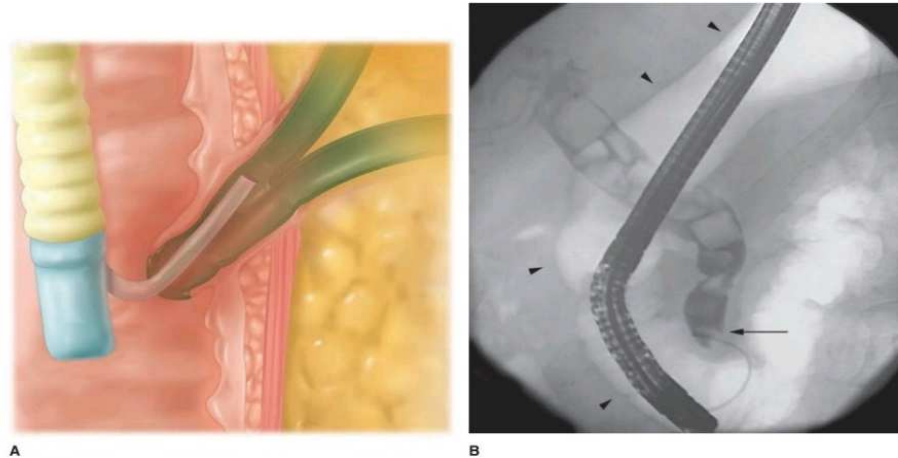


FIGURE 19 : ENDOSCOPIC RETROGRADE CHOLANGIOGRAPHY : A. Side viewing endoscope in duodenum and catheter in CBD. B. An endoscopic cholangiogram showing CBD stones.

DIAGNOSIS OF ACUTE CHOLECYSTITIS

Based on symptoms and physical signs a diagnosis of acute cholecystitis can be made.

- Ultrasonography is the initial investigation of choice to confirm diagnosis.
- A MRCP can be done to rule out choledocholithiasis if stones in common bile duct are suspected.
- If there is any concern about complications of cholecystitis like perforation then a CT scan can be done.
- Tokyo guidelines are used for severity grading of acute cholecystitis.

TREATMENT

1. Conservative management :

For patients with asymptomatic gall stones , observation to be done till symptoms appear.

Indications of Prophylactic Cholecystectomy :

- a. Diabetic patients
- b. Congenital haemolytic anemia
- c. Patient undergoing bariatric surgery , since they have shown risk of increased symptoms.

In >90% patients , conservative management yields good results.

- a. Nil per oral till pain resolves.
- b. Intravenous fluids administration
- c. Analgesics
- d. Broad spectrum Antibiotic coverage
- e. Once the signs of active inflammation subsides , clear liquids are started followed by regular diet^{8,9}.

2. LAPAROSCOPIC CHOLECYSTECTOMY

The timing of cholecystectomy for acute cholecystitis is debated as many surgeons prefer and early intervention within 5 to 7 days of onset of symptoms. Good outcome can be gained in early cholecystectomy if surgeon is experienced and hospital facilities are good.

A surgeon should plan surgery after 6 weeks of initial attack till inflammation relieves. The conversion rate from laparoscopic to open is more in acute cases than in elective cases.

STEPS OF LAPAROSCOPIC CHOLECYSTECTOMY:

1. Patient is positioned comfortably in a supine position with his both arms by side and feet strapped to secure his position.
2. General Anesthesia is preferred in all laparoscopic cholecystectomy cases.
3. After intubation, foley's catheter and ryles tube insertion is done.
4. Pneumoperitoneum is necessary to create a working space in peritoneal cavity. It is maintained at pressure level of 15mmHg.

2 techniques are known to create pneumoperitoneum¹³ :

a. Veress needle / closed technique =

Veress needle is slid through the anterior abdominal wall along the umbilicus, position is confirmed by normal saline using a plunger less syringe. CO2 insufflation is done at rate of 2 litre/min. Intraabdominal position is confirmed by seeing uniform abdominal distension.

b. Open Hassan's technique = In this the pneumoperitoneum is created under direct vision by taking incision supraumbilical and opening in layers. After entering peritoneum, 10mm trocar is inserted and secured in place with sutures. Further CO2 insufflation is done.

A. Placement of Ports and adequate Exposure :

In the periumbilical region, a 5 or 10mm port is placed. Using a 0 or 30 degree laparoscope, abdominal cavity including gall bladder, omentum, liver, bowel and pelvis are inspected to look for adhesions or other pathologies.

Under direct vision, the additional 5mm ports are placed in right midclavicular line, one in right anterior axillary line 2cm below costal margin and one in right upper quadrant.

Patient is given reverse trendelenberg position with a left tilt of 15 degrees allowing colon and omentum to move away from surgical site.

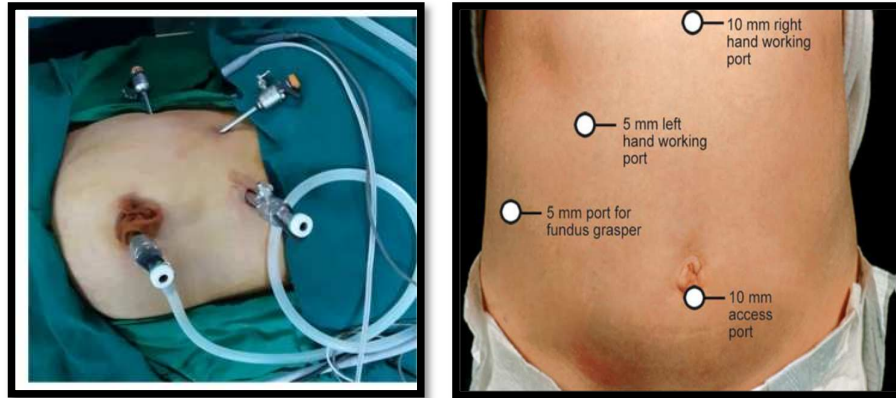


FIGURE 20: LAPAROSCOPIC PORT PLACEMENT FOR CHOLECYSTECTOMY

B. Porta hepatis Exposure :

Using an atraumatic grasper , the fundus of gallbladder is lifted and retracted upwards towards right shoulder. It gives adequate view of calot's triangle and liver for dissection. Any adhesions if present between liver , gallbladder are separated from fundus towards neck of gallbladder using blunt dissection and cautery.

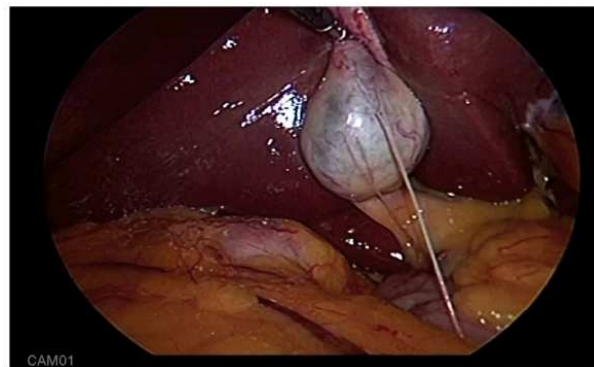


FIGURE 21 : PORTA HEPATIS EXPOSURE

C. Calot's Triangle Dissection :

After retraction of infundibulum laterally for better visualization , the peritoneal layer over neck of gall bladder is exposed and opened using cautery.

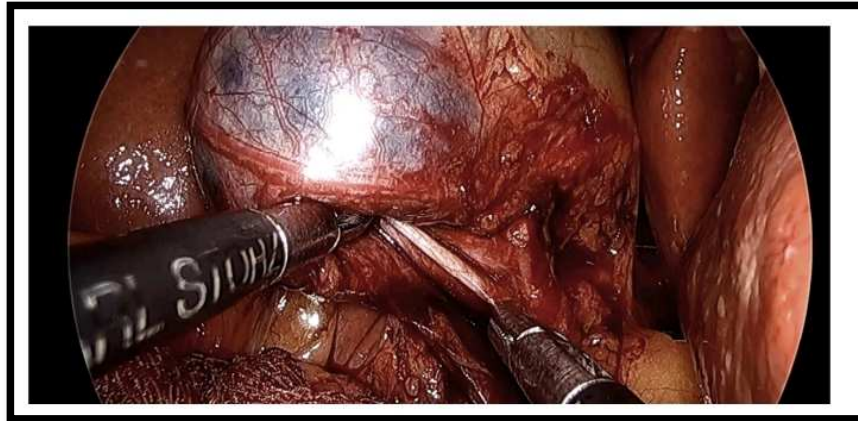


FIGURE 22 : CALOT'S TRIANGLE DISSECTION

D. Obtaining critical View of safety¹⁴ :

Complete dissection of Calot's triangle with separation of infundibulum from liver bed will prevent inadvertent bile duct injuries. Dissection in Calot's triangle should be such that only two structures are seen passing to the gallbladder which are cystic artery and cystic duct. While ligating the cystic duct , two clips are put on duct side and one over gallbladder side. Milking of stones present in cystic duct towards the gallbladder is done before application of clips. Cystic artery is ligated before cystic duct.

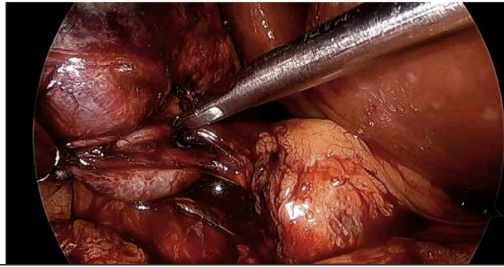


FIGURE 23 A: CLIPPING OF CYSTIC ARTERY

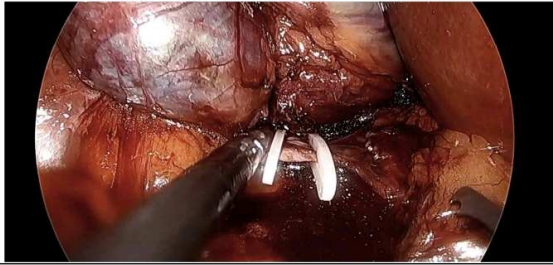


FIGURE 23 B: CLIPPING OF CYSTIC DUCT

E. Detachment of gallbladder from fossa :

Cystic plate is exposed after dissection of gall bladder fossa from its bed by monopolar hook cautery. If there is iatrogenic spillage of bile due to gall bladder perforation then it can be controlled by tie or grasping. Irrigation and suction of bile should be done immediately. Haemostasis should be confirmed and position of clips to be checked again.

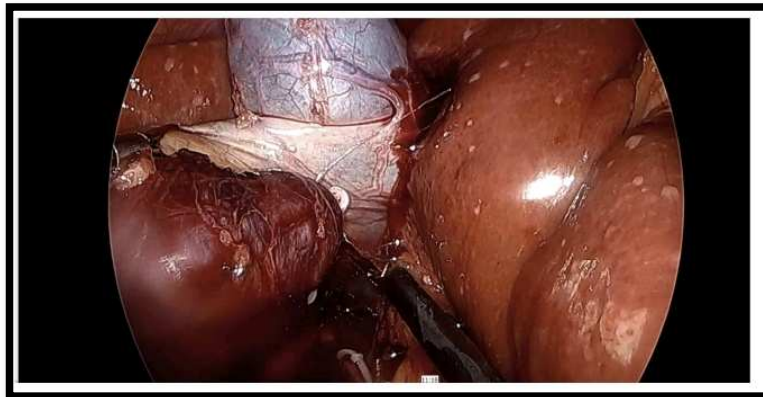


FIGURE 24 : DETACHING GALL BLADDER FROM FOSSA

F. Extraction of gallbladder specimen :

Camera is placed in subxiphoid port and gallbladder after placing in endobag is removed from umbilical port.



FIGURE 25 : GALLBLADDER SPECIMEN AFTER EXTRACTION

G. Inspection and irrigation :

After extraction of gallbladder, port placed back to look for any bleeding. Thorough saline wash to gallbladder fossa and paracolic gutter is given.

H. Drainage and closure :

A drain is placed if bleeding from liver bed suspected and in case of iatrogenic bile spillage through gall bladder perforation.

CONVERSION TO OPEN SURGERY : In cases of acute severe cholecystitis due to increased oedema of gall bladder wall , friability of structures and dense adhesions , inability to tolerate pneumoperitoneum^{15,16}.

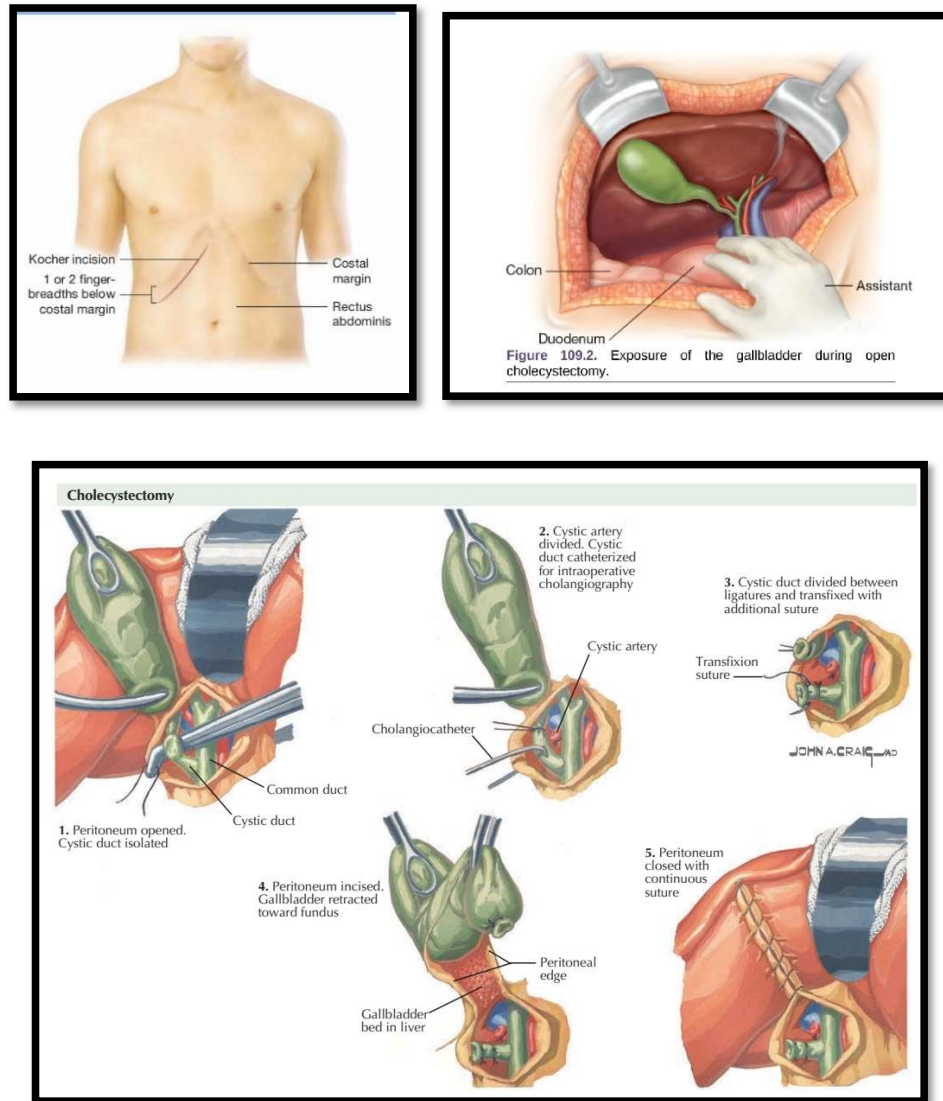


FIGURE 26 : OPEN CHOLECYSTECTOMY

PERCUTANEOUS TRANSHEPATIC CHOLECYSTOSTOMY DRAINAGE :

In cases where patients are physically unfit for cholecystectomy , a cholecystostomy tube is placed in the gallbladder for decompression and drainage for distended , inflamed , purulent or hydropic gallbladder.

Under ultrasound guidance , percutaneous transhepatic cholecystostomy tubes are inserted. Catheter is passed through layers of abdominal wall , liver and gall bladder. Passage of catheter through liver prevents uncontrolled bile leak in the peritoneal cavity.

The catheter can be later taken off when patient condition improves and inflammation settles down. Interval cholecystectomy should be considered after optimising patient for surgery^{8,9}.

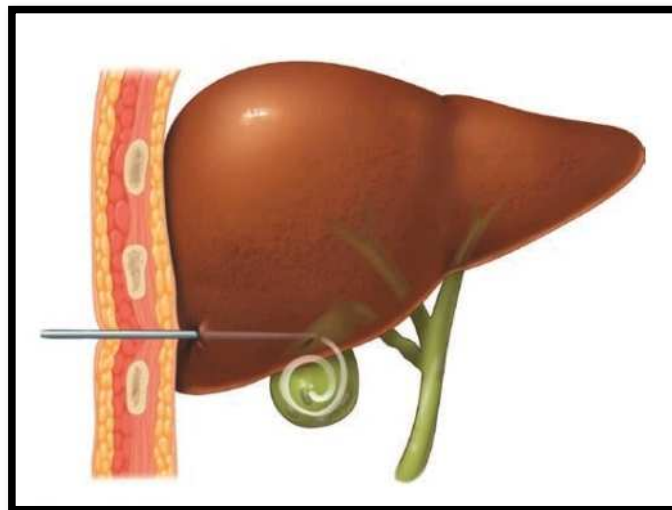


FIGURE 30 : PERCUTANEOUS CHOLECYSTOSTOMY . PIG TAIL CATHETER BEING INSERTED IN GALL BLADDER.

NORMAL HAEMATOPOEISIS

In the 3rd week of embryonic development, progenitors of blood cells appear in the yolk sac. Hematopoietic Stem Cells migrate to liver in 3rd month of gestation and thus liver becomes chief site of blood cells formation till just before birth.

In 4th month of gestation, bone marrow becomes major site of HSCs. By birth, marrow throughout the skeleton is hematopoietically active, and hepatic hematopoiesis become inactive soon after birth. After puberty, hematopoiesis ceases in distal bones and becomes restricted to the axial skeleton. The formed elements of blood—red cells, granulocytes, monocytes, platelets, and lymphocytes—have a common origin from HSCs, pluripotent cells that sit at the apex of a hierarchy of bone marrow progenitors.

HSCs give rise to several kinds of early progenitor cells that have more restricted differentiation potential, such that they ultimately produce mainly myeloid cells or lymphoid cells¹⁸.

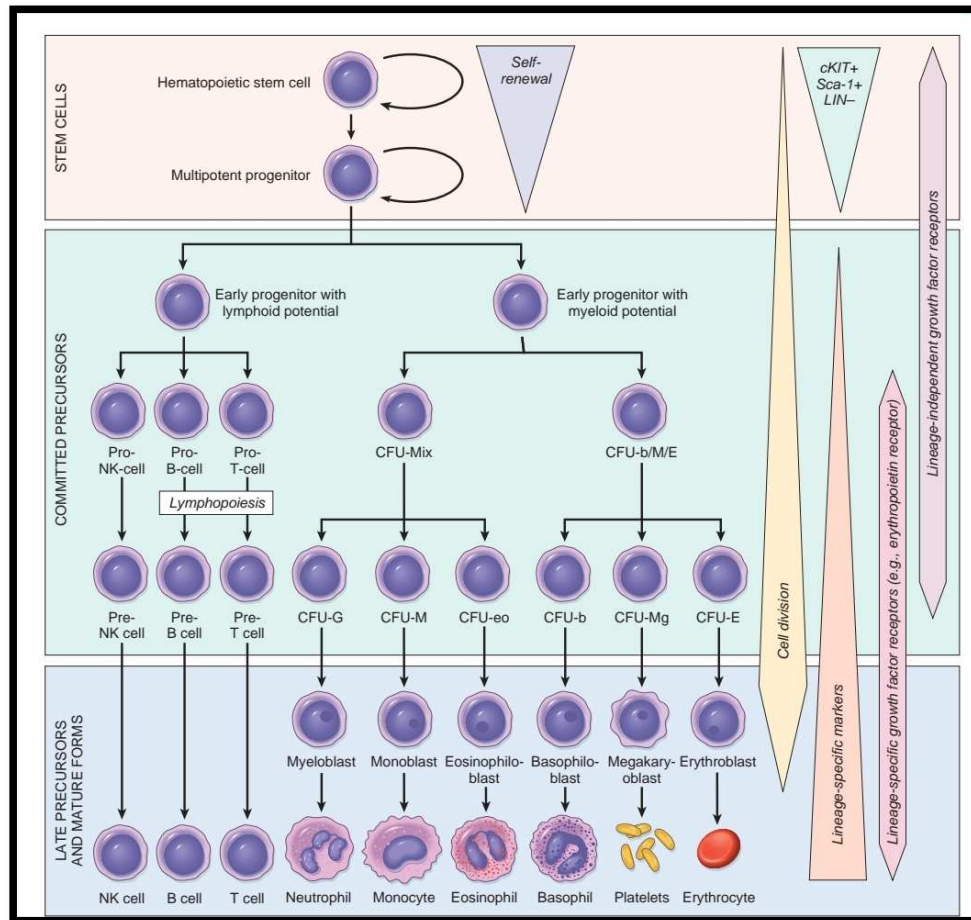


FIGURE 31 : DIFFERENTIATION OF BLOOD CELLS

LYMPHOPOEISIS

1. Immunocompetent cells : Lymphocytes , plasma cells
2. Primary site of lymphopoiesis : bone marrow , thymus
3. Other sites: Spleen ,lymphoid tissue in gut , lymph nodes.

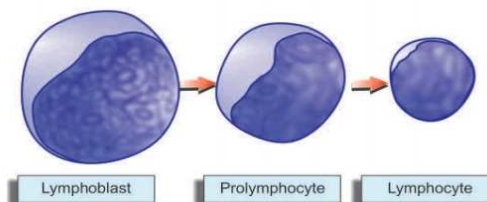


FIGURE 32 : FORMATION OF LYMPHOID SERIES OF CELLS

LYMPHOID SERIES

1. LYMPHOBLAST :

- Earliest precursor
- 10-18 μm in diameter
- Containing a large round to oval nucleus having slightly clumped or stippled nuclear chromatin. The nuclear membrane is denser and the number of nucleoli is fewer.
- Cytoplasm is less and basophilic.

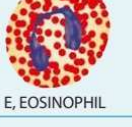
3. PROLYMPHOCYTE

- It is intermediate between the lymphoblast and mature lymphocyte.
- 9-18 μm in diameter
- Round to indented nucleus with slightly stippled or coarse chromatin and may have 0-1 nucleoli.

4. LYMPHOCYTE

- Small lymphocytes (9-12 μm) and large lymphocytes(12-16 μm)
- Clumped chromatin
- less cytoplasm(basophilic)

MATURE LEUCOCYTES =

Morphology and functions of inflammatory cells.		
MORPHOLOGY	FEATURES	MEDIATORS
 A, POLYMORPH	i. Initial phagocytosis of bacteria and foreign body ii. Acute inflammatory cell	i. Primary granules (MPO, lysozyme, cationic proteins, acid hydrolases, elastase) ii. Secondary granules (lysozyme, alk. phosph, collagenase, lactoferrin) iii. Tertiary granules (gelatinase, cathepsin) iv. Reactive oxygen metabolites
 B, MONOCYTE/MACROPHAGE	i. Bacterial phagocytosis ii. Chronic inflammatory cell iii. Regulates lymphocyte response	i. Acid and neutral hydrolases (lysosomal) ii. Cationic protein iii. Phospholipase iv. Prostaglandins, leukotrienes v. IL-1
 C, LYMPHOCYTE	i. Humoral and cell-mediated immune responses ii. Chronic inflammatory cell iii. Regulates macrophage response	i. B cells: antibody production ii. T cells: delayed hypersensitivity, cytotoxicity
 D, PLASMA CELL	i. Derived from B cells ii. Chronic inflammatory cell	i. Antibody synthesis ii. Antibody secretion
 E, EOSINOPHIL	i. Allergic states ii. Parasitic infestations iii. Chronic inflammatory cell	i. Reactive oxygen metabolites ii. Lysosomal (major basic protein, cationic protein, eosinophil peroxidase, neurotoxin) iii. PGE ₂ synthesis
 F, BASOPHIL/MAST CELL	i. Receptor for IgE molecules ii. Electron-dense granules	i. Histamine ii. Leukotrienes iii. Platelet activating factor

1. POLYMORPHS (NEUTROPHILS)

- 12-15 μm in diameter.
- Nucleus dense , having 2-5 lobes
- Pale cytoplasm with violet granules
- Types of Lysosomal granules : Primary and secondary¹⁹

FUNCTIONS OF NEUTROPHILS:

1. **Chemotaxis** : The cells are drawn towards inflammatory site.
2. **Phagocytosis** : neutrophils eat up foreign particles
3. **Killing** microorganisms : O₂ dependent and independent mechanisms

Neutrophil leucocytosis: Count >7,500/ μ l , reactionary to bacterial infections which are acute in nature.

Seen in localized or generalized acute infections, local or generalized by bacteria ,fungi, parasites etc.(eg:cholecystitis, Appendicitis) , tissue damage resulting from operations, gout, Acute haemorrhage , hemolysis , collagen-vascular diseases, malignancies , hypersensitivity reactions , Myeloproliferative disorders ,uraemia¹⁹

LYMPHOCYTES MORPHOLOGY

- Small lymphocytes (8-12 μ m) and large lymphocytes (12-16 μ m)
- Round nucleus
- coarsely-clumped chromatin
- scanty basophilic cytoplasm.
- B lymphocytes secrete plasma cells after stimulus
- 3 types of lymphocytes:

A. T lymphocytes – They grow in the thymus and are also known as thymocytes.

They are mainly involved in direct action on antigens and are therefore involved in cell-mediated immune (CMI) reaction by its subsets such as cytotoxic (killer) T cells (CD3+), CD8+ T cells, and delayed hypersensitivity reaction by CD4+ T cells.

B. B lymphocytes – Humoral immunity - bone marrow derived and also include plasma cells- specific immunoglobulin antibodies.

C. NK cells i.e. natural killer cells – Innate immunity - cause lysis of foreign body.

LYMPHOCYTOSIS :is termed lymphocytosis, while absolute lymphocyte count below 1,500/ μm is referred to as lymphopenia.

Lymphocytosis (Above 11,000/ μm)

Infections e.g. tuberculosis, infectious mononucleosis, viral hepatitis, secondary syphilis , lymphocytic leukaemias, lymphoma.

Lymphopenia Lymphopenia is uncommon and occurs in

the following conditions : Irradiation , steroid therapy , Most acute infections etc¹⁸

ACUTE INFLAMMATION

I. Vascular events

II. Cellular events

I. VASCULAR EVENTS

Earliest response towards any tissue damage is changes in arterioles, veins, capillaries causing changes in hemodynamics and permeability of vasculature.

Changes in hemodynamics:

1. **Transient vasoconstriction** of capillaries and arterioles : within 2-5 seconds –
Lasts for 5min
2. **Persistent progressive vasodilatation of arterioles**
3. **Raised viscosity of blood due to slow microcirculation**
4. **Margination** : leucocytes migrate from the gaps between the endothelial cells
out of vascular walls

Altered vascular Permeability^{18,19} :

PATHOGENESIS

In and around the inflamed tissue, there is accumulation of oedema fluid in the interstitial compartment which comes from blood plasma by its escape through the endothelial wall of peripheral vascular bed. In the initial stage, the escape of fluid is due to vasodilatation and consequent elevation in hydrostatic pressure. This is transudate in nature.

PATTERNS OF INCREASED VASCULAR PERMEABILITY

- i) Contraction of endothelial cells**
- ii) Contraction or mild endothelial damage**
- iii) Direct injury to endothelial cells**
- iv) Leucocyte-mediated endothelial injury**
- v) Leakiness in neovascularisation**

II. CELLULAR EVENTS

The cellular phase of inflammation consists of 2 processes:

- 1. exudation of leucocytes; and
- 2. phagocytosis.

A. Exudation of Leucocytes

The escape of leucocytes from the lumen of microvasculature to the interstitial tissue is the most important feature of inflammatory response. In acute inflammation, polymorphonuclear neutrophils (PMNs) comprise the first line of body defence, followed later by monocytes and macrophages.

1. MARGINATION AND PAVEMENTING

During initial stage of inflammation, blood flow first increases and then there is slowing → leucocytes occupy the central zone and the plasma forms peripheral zone, known as margination. The neutrophils in central zone align together which is known as pavementing.

2. ROLLING , ADHESION

The following cell adhesion molecules (CAMs) participate in rolling and adhesion stages :

i) **Selectins**

ii) **Integrins**

iii) **Immunoglobulin gene superfamily adhesion molecules.**

- a. Intercellular adhesion molecule-1
- b. Platelet-endothelial cell adhesion molecule-1 (PECAM-1)

3. EMIGRATION: Peripherally arranged leucocytes damage the basement membrane with collagenases and move out into extravascular space.

3. CHEMOTAXIS The transmigration of leucocytes after crossing several barriers to reach the interstitial tissues is a chemotactic factor-mediated process called chemotaxis.

The following agents act as potent chemotactic substances for neutrophils:

- i) Leukotriene B₄
- ii) Components of complement system (C5a and C3a)
- iii) Cytokines
- iv) Soluble bacterial products

5. PHAGOCYTOSIS

Phagocytosis is defined as the process of engulfment of solid particulate material by the cells. There are 2 main types of phagocytic cells:

i) Polymorphonuclear neutrophils (PMNs) which appear early in acute inflammatory response, sometimes called a microphages.

ii) Circulating monocytes and fixed tissue mononuclear phagocytes, commonly called as macrophages.

Phagocytosis of the microbe by polymorphs and macrophages involves the following 3 steps:

1. Recognition and attachment
2. Engulfment
3. Killing and degradation

1. RECOGNITION AND ATTACHMENT

Phagocytosis is initiated by the expression of cell surface receptors on macrophages which recognise microorganisms: mannose receptor and scavenger receptor. They are covered by opsonins.

2. ENGULFMENT

There is formation of cytoplasmic pseudopods surrounding opsonized particle. Later the plasma membrane breaks from surface of cell and it gets internalised into the cell.

3. KILLING AND DEGRADATION

The microorganisms after being killed by antibacterial substances are degraded by hydrolytic enzymes. Mechanisms involved :

A. Intracellular mechanisms:

i) Mechanism mediated by oxygen free radicals : Oxidative bactericidal mechanism

Myeloperoxidase dependent and independent pathways

ii) By lysosomal granules : Oxidative mechanism

iii) Non-oxidative bactericidal mechanism

B. Extracellular Mechanisms:

B. EXTRACELLULAR MECHANISMS Following mechanisms

explain the bactericidal activity at extracellular level:

i) Granules Degranulation of macrophages and neutrophils continues to exert its effects of proteolysis outside the cells as well.

ii) Immune mechanisms : immune-mediated lysis of microbes takes place outside the cells by mechanisms of cytolysis, antibody mediated lysis and by cell-mediated cytotoxicity.

MEDIATORS OF INFLAMMATION

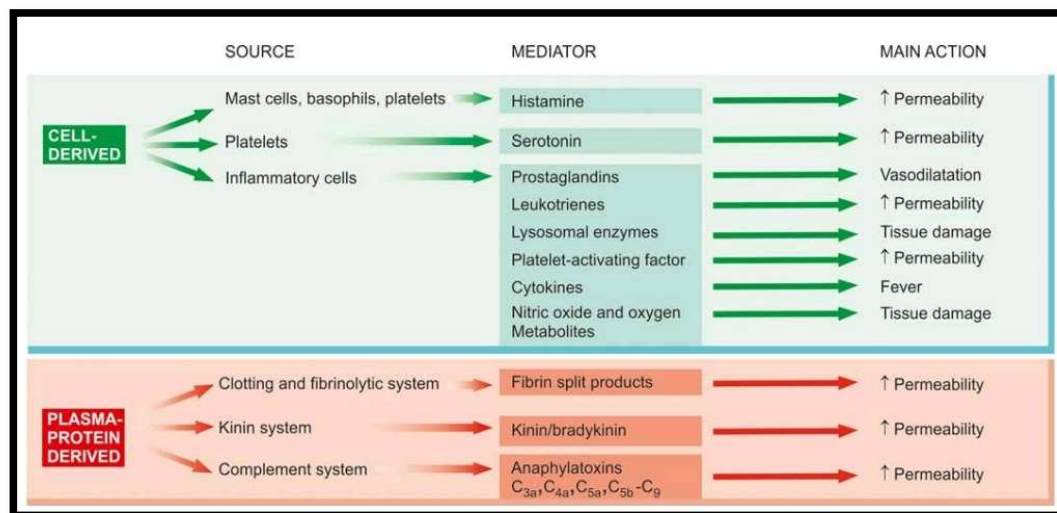
I. CELL-DERIVED MEDIATORS

1. Vasoactive amines (Histamine, 5-hydroxytryptamine, neuropeptides)
2. Arachidonic acid metabolites (Eicosanoids)
 - i. Metabolites via cyclo-oxygenase pathway (prostaglandins, thromboxane A₂, prostacyclin, resolvins)
 - ii. Metabolites via lipo-oxygenase pathway (5-HETE, leukotrienes, lipoxins)
3. Lysosomal components (from PMNs, macrophages)
4. Platelet activating factor
5. Cytokines (IL-1, IL-6, IL-8, IL-12, IL-17, TNF- α , TNF- β , IFN- γ , chemokines)
6. Free radicals (Oxygen metabolites, nitric oxide)

II. PLASMA PROTEIN-DERIVED MEDIATORS (PLASMA PROTEASES)

Products of:

1. The kinin system
2. The clotting system
3. The fibrinolytic system
4. The complement system



MAJOR CYTOKINES AND THEIR ROLE IN INFLAMMATION:

CYTOKINE	CELL SOURCE	CELL TARGET	MAIN ACTIONS
IL-1	Monocytes/macrophages, B cells, fibroblasts, endothelial cells, some epithelial cells	All cells	• Expression of adhesion molecules • Emigration of neutrophils and macrophages • Role in fever and shock • Hepatic production of acute phase protein
IL-6	Same as for IL-1	T and B cells, Epithelial cells, hepatocytes, Monocytes/macrophages	• Hepatic production of acute phase protein • Differentiation and growth of T and B cells
IL-8	Monocytes/macrophages, T cells, neutrophils, fibroblasts, endothelial cells, epithelial cells	Neutrophils, basophils, T cells, monocytes/macrophages, endothelial cells	• Induces migration of neutrophils, macrophages and T cells • Stimulates release of histamine from basophils • Stimulates angiogenesis
IL-12	Macrophages, dendritic cells, neutrophils	T cells, NK cells	• Induces formation of T helper cells and killer cells • Promotes CTL cytolytic activity • Increases production of IFN-γ • Decreases production of IL-17
IL-17	CD4+T cells	Fibroblasts, endothelial cells, epithelial cells	• Increases secretion of other cytokines • Migration of neutrophils and monocytes
TNF- α	Monocytes/macrophages, mast cells/basophils, eosinophils, B cells, T cells, NK cells	All cells except RBCs	• Hepatic production of acute phase protein • Systemic features (fever, shock, anorexia) • Expression of endothelial adhesion molecules • Enhanced leucocyte cytotoxicity • Induction of pro-inflammatory cytokines
IFN- γ	T cells, NK cells	All cells	• Activation of macrophages and NK cells • Stimulates secretion of Igs by B cells • Differentiation of T helper cells
MCP-1	Fibroblasts, smooth muscle cells, blood mononuclear cells	Monocytes/macrophages, NK cells, T cells	• Chemoattractant for monocytes, T cells and NK cells • Stimulates release of histamine from basophils
Eotaxin	Alveolar cells, myocardium	Eosinophils, basophils	• Chemoattractant for eosinophils and Basophils • Induces allergic pulmonary disease
PF-4	Platelets, megakaryocytes	Fibroblasts, endothelial cells	• Chemoattractant for fibroblasts • Inhibitory to haematopoietic precursors and endothelial cell proliferation

IL=interleukin; TNF=tumour necrosis factor; IFN=interferon; MCP=monocyte chemotactic protein; PF=platelet factor.

MATERIALS AND METHODS

This was a prospective observational study conducted in Department of General Surgery in KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, KAHER, Belagavi for duration of 1 year from January 2021 to December 2021.

Source of data:

Patients presenting with clinical features of acute cholecystitis to surgery outpatient department and emergency department of KLES Dr. Prabhakar Kore hospital and MRC, KAHER, Belagavi.

Inclusion criteria :

All cases of acute cholecystitis with Age > 18years.

Exclusion criteria :

1. Severe systemic infection
2. Immunocompromised state
3. Elective cholecystectomy cases
4. Taken antibiotics 7 days before visit
5. Pregnant and Lactating mothers

Sample size = 110

Sampling procedure = Sample size Using G*Power software sample size is calculated, Sample size is calculated by below formula, $n = (Z_{1-\alpha/2} + Z_{1-\beta})^2 p_0(1-p_0) / b^2$ In the above formula, p_0 is given as, $p_0 = P(y=1|x=\mu x)$. Suppose logistic regression model has more than one independent variables (predictors), then sample size can be estimated as, $n^* = n / (1 - R^2)$ Where R^2 is the value calculated by regressing the independent variable of prime interest on all the other independent variables (using multiple linear regression). Power of the study assumed as 90%, with 95% confidence level, p_0 is assumed as 0.5, R^2 as 0.8, hence

minimum sample size required is 52. In view of availability of cases and to increase validity of this study, sample size was taken as 110.

Statistical Analysis = Data collected and stored in Microsoft Excel. Data analyzed using statistical software R developed by R foundation for statistical computing. Continuous variables given in mean $\pm$ SD/median (range). Categorical variables represented by frequency. To check the dependency between attributes Chi-square test was used. P-value less than or equal to 0.05 shows statistical significance.

Procedure:

1. Informed consent was taken from all participants.
2. NLR was calculated at the time of admission as the absolute neutrophil count divided by the absolute lymphocyte count
3. WBC and CRP levels were also checked on presentation.
4. CT scan / ultrasonography investigation was done within 6 hours of presentation.
5. Receiver Operating Characteristic (ROC) analysis was performed to identify the most useful NLR cut-off value in relation to the severity of cholecystitis.
6. Demographic data and clinical characteristics of the patients were collected at the time of their visit to outpatient department / emergency department. A. Age B. Gender C. Initial vital signs (blood pressure, heart rate, respiratory rate, and temperature); D. final diagnosis; E. cholecystectomy operation F. ICU admission G. duration of hospital stay H. histopathology reports were recorded. I. Clinical findings, including fever; duration of symptoms; right upper quadrant (RUQ) pain; epigastric pain; Murphy's sign; diffuse abdominal pain; and early blood examination (WBC count, neutrophil count, neutrophil-to-lymphocyte ratio [NLR], platelet, aspartate aminotransferase

[AST], alanine transaminase [ALT], CRP, erythrocyte sedimentation rate [ESR], protein, albumin, and prothrombin time (INR), were obtained within 2 h of arrival. Pus culture sensitivity if pigtail insertion done.

5. Postoperative complications

8. Calculous or acalculous cholecystitis

9. BMI

ASSESSMENT

All patients were divided into 3 groups on the basis of clinical findings and Tokyo guidelines.

Clinically, severe AC is as defined as the presence of pathologic gangrenous, necrotizing, suppurative, and perforated cholecystitis. They will be classified according to the 2007 Tokyo Guidelines (TG07) revised in 2013 and then 2018 for diagnosing severe AC .

TOKYO CONSENSUS GUIDELINES FOR SEVERITY GRADING OF ACUTE CHOLECYSTITIS ⁵

Grade III (severe) acute cholecystitis	
Associated with dysfunction of any one of the following organs/systems:	
1 Cardiovascular dysfunction	Hypertension requiring treatment with dopamine $\leq 5 \mu\text{g/kg/min}$, or any dose of norepinephrine (noradrenaline)
2 Neurological dysfunction	Decreased level of consciousness
3 Respiratory dysfunction	P_aO_2/FiO_2 ratio < 300
4 Renal dysfunction	Oliguria; creatinine $> 2.0 \text{ mg/dL}$
5 Hepatic dysfunction	Prothrombin time (PT-INR) > 1.5
6 Haematological dysfunction	Platelet count $< 100\,000/\text{mm}^3$
Grade II (moderate) acute cholecystitis	
Associated with any one of the following conditions:	
1 Elevated white cell count ($> 18\,000/\text{mm}^3$)	
2 Palpable tender mass in the right upper abdominal quadrant	
3 Duration of complaints > 72 hours	
4 Marked local inflammation (gangrenous cholecystitis, pericholecystic abscess, hepatic abscess, biliary peritonitis, emphysematous cholecystitis)	
Grade I (mild) acute cholecystitis	
Does not meet the criteria of grade II or grade III acute cholecystitis. Grade I can also be defined as acute cholecystitis in a healthy person with no organ dysfunction and mild inflammatory changes in the gallbladder, making cholecystectomy a safe and low-risk operative procedure	

Radiological diagnosis of cholecystitis ⁶

A. CT findings :

Diagnosis	Computed tomography findings
• Acute calculus cholecystitis	Gallstone in the gallbladder neck or cystic duct, thickened ($\geq 0.3 \text{ cm}$) and enhancing wall, pericholecystic fat stranding with or without pericholecystic fluid, reactive enhancement in the adjacent liver
• Gangrenous cholecystitis	Nonenhancing wall, sloughed membranes, mural striation, irregular enhancing wall with defect, with or without gallstone, pericholecystic fat stranding and fluid (more than that seen in uncomplicated cholecystitis)
• Emphysematous cholecystitis	Similar findings to acute cholecystitis, with presence of gas in the gallbladder wall (intraluminal gas can be due to fistula formation or other causes of pneumobilia)
• Perforated cholecystitis	Similar findings to acute cholecystitis, with focal defect in the gallbladder wall, contiguous pericholecystic fluid or hepatic abscess

B. USG Findings:**Gallbladder wall**

- Thickness ≥ 0.3 cm is considered thickened
- Enhancement Poor enhancement or irregular enhancement
- Continuity Focal wall defect suggests gangrenous cholecystitis; focal defect with contiguous pericholecystic fluid suggests perforated cholecystitis
- Irregularity of wall Irregularity is a sign of acute cholecystitis
- Gas Intramural gas is a sign of emphysematous cholecystitis

Gallbladder lumen

- Gallstone Usually at the gallbladder neck
- Gas Cholecystoenteric fistula with or without ileus
- High-density fluid Haemorrhagic fluid from gangrenous cholecystitis or gallbladder empyema
- Sloughed mucosa Considered as a specific sign of gangrenous cholecystitis

Pericholecystic space

- Fat stranding Hallmark of gallbladder inflammation
- Fluid Small amount is usually present in uncomplicated acute cholecystitis; large amount is a red flag for gangrenous or perforated cholecystitis
- Abscess Pericholecystic abscess suggests gangrenous or perforated cholecystitis

Liver, peritoneal cavity and bowel

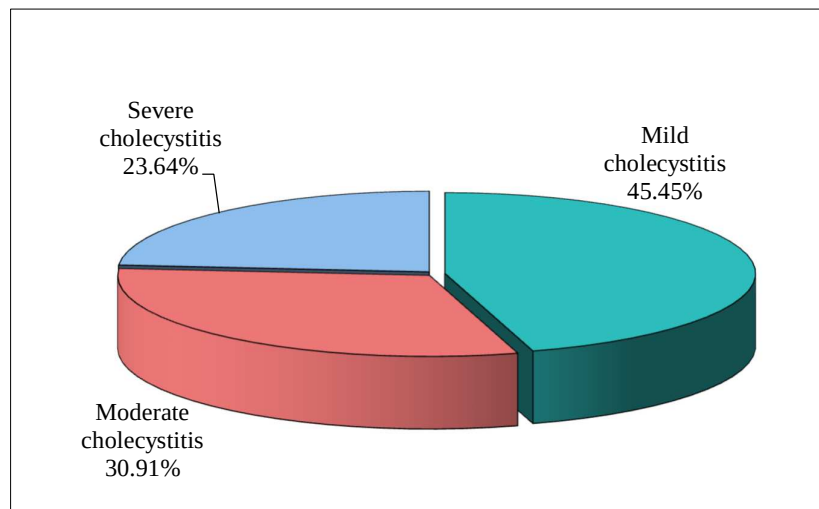
- Reactive hyperaemia in adjacent liver Sign of inflammation of the gallbladder (almost always seen)
- Liver abscess Small to huge, secondary to gallbladder perforation
- Peritoneal collection Large collection suggests perforated cholecystitis
- Dilated small bowel Presence suggests gallstone ileus

RESULTS

1. Grades of acute cholecystitis in the study

SEVERITY OF ACUTE CHOLECYSTITIS	NUMBER	%
Mild cholecystitis	50	45.45
Moderate cholecystitis	34	30.91
Severe cholecystitis	26	23.64
Total	110	100.0

Figure: Severity of acute cholecystitis in the study

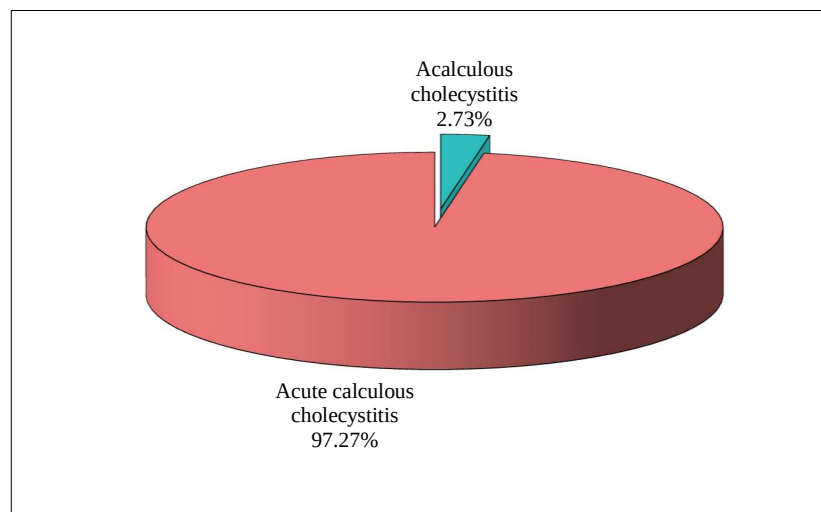


- Out of total 110 patients , 23.64% had severe acute cholecystitis , 30.91% had moderate and 45.45% has mild cholecystitis based on Tokyo guidelines classification.

2. Types of cholecystitis

Diagnosis	Number	%
Acalculous cholecystitis	3	2.73
Acute calculous cholecystitis	107	97.27
Total	110	100.0

Figure: Pie chart - Types of cholecystitis

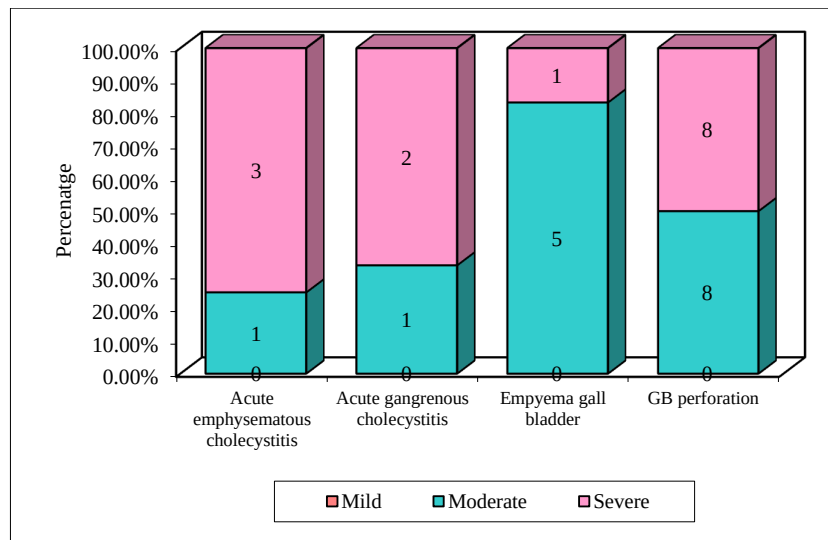


- A total of 3(2.73%) patients had acute acalculous cholecystitis and rest were cases of calculous cholecystitis (97.27%).

3. Secondary complications seen in different grades of acute cholecystitis :

Secondary complications	Mild	%	Moderate	%	Severe	%	Total	% of total complications
Acute emphysematous cholecystitis	0	0.00	1	25.00	3	75.00	4	13.7
Acute gangrenous cholecystitis	0	0.00	1	33.33	2	66.67	3	10.3
Empyema gall bladder	0	0.00	5	83.34	1	16.67	6	20.68
GB perforation	0	0.00	8	50.00	8	50.00	16	55.17

Figure: BAR DIAGRAM SHOWING SECONDARY COMPLICATIONS IN ACUTE CHOLECYSTITIS



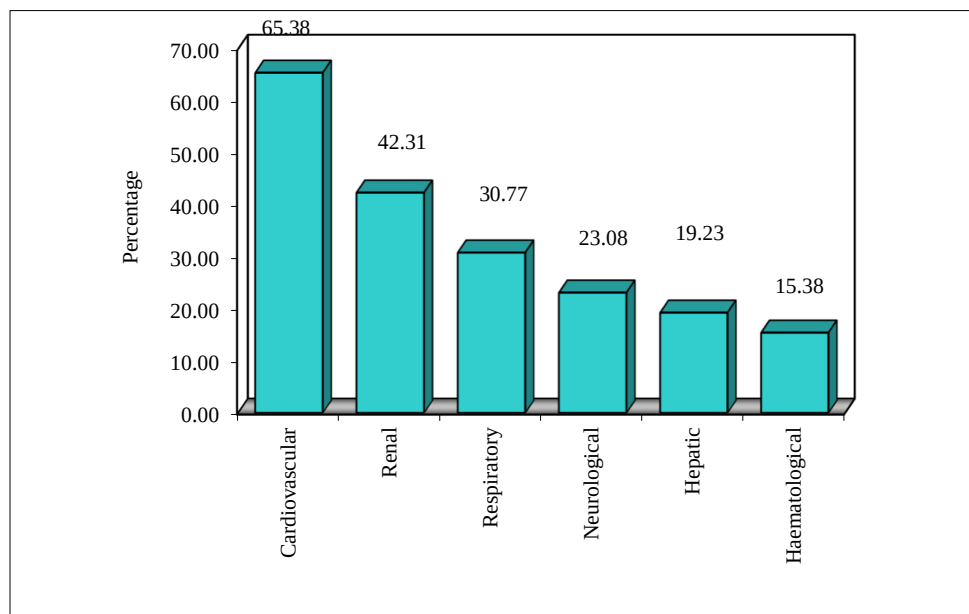
- Acute emphysematous changes were present in 4 patients (13.7%) out of which 1 patient belonged to moderate acute cholecystitis group and 3 patients belonged to severe acute cholecystitis group.
- Acute gangrenous cholecystitis was seen in total 3 patients (10.3%) out of which 1 patient was from moderate group and 2 patients from severe group.

- Empyema gall bladder was seen in total 6 patients (20.68%) out of which 5 patients were of moderate acute cholecystitis and 1 patient of severe group.
- Gall bladder perforation was present in 8 cases of moderate cholecystitis and 8 cases of severe cholecystitis, thus total 16 cases accounting to 55.17% of total complications.

4. Criteria involved in diagnosis of Severe Acute cholecystitis

Criteria of dysfunction	Severe acute cholecystitis	%
Cardiovascular	17	65.38
Neurological	6	23.08
Respiratory	8	30.77
Renal	11	42.31
Hepatic	5	19.23
Haematological	4	15.38

Figure: Severity of acute cholecystitis by criteria involved

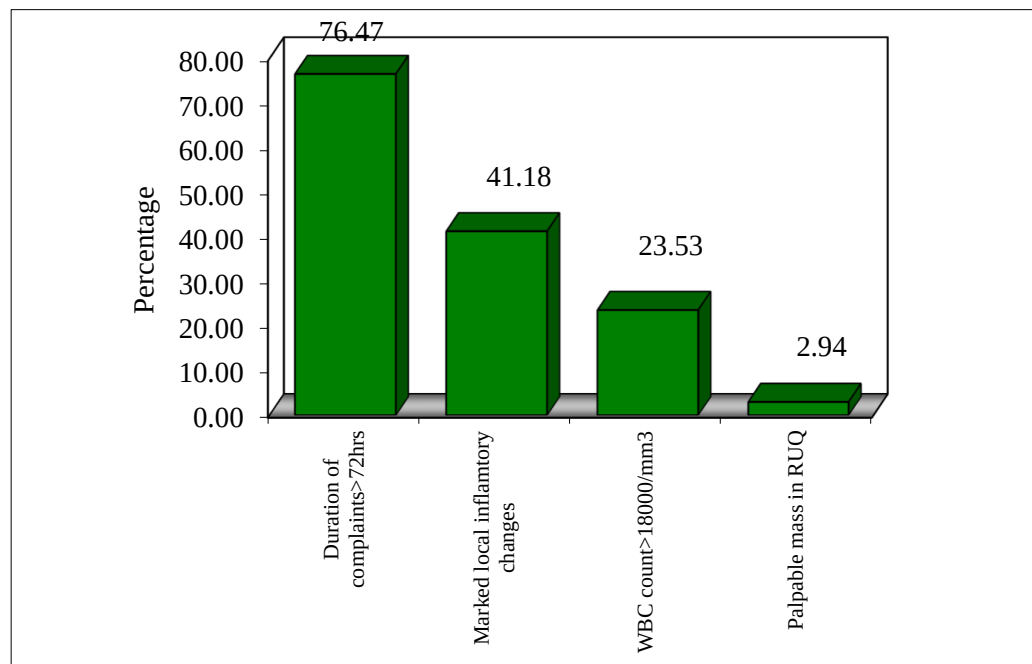


- 6 components are present in Tokyo guidelines, the presence of which will make a diagnosis of severe acute cholecystitis.
- As per our study, 17 patients (65.38%) had secondary dysfunction of cardiovascular system , 6 patients (23.08%) had a effect on neurological system , 8 patients(30.77) had effect on respiratory system , 11 (42.31%) on renal system , 5 patients(19.23%) on hepatic system , 4 patients(15.38%) on haematological system.

5. Criteria of dysfunction in moderate group

Criteria of dysfunction	Moderate acute cholecystitis	%
WBC count>18000/mm ³	8	23.53
Palpable mass in RUQ	1	2.94
Duration of complaints>72hrs	26	76.47
Marked local inflammatory changes	14	41.18

Figure: Criteria of dysfunction in moderate group

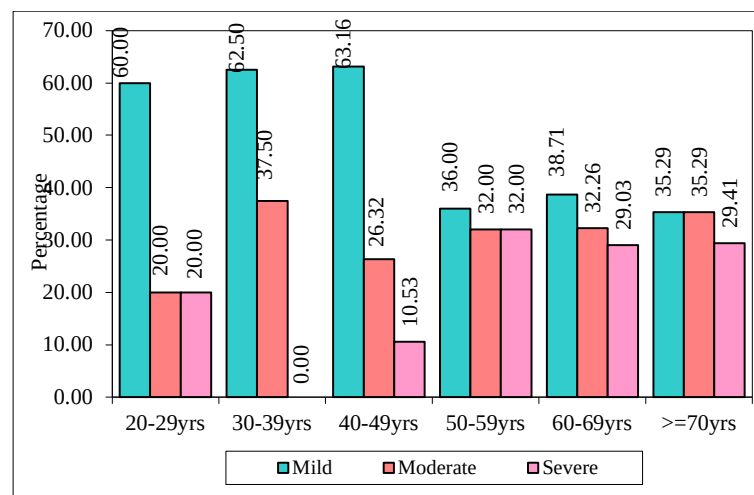


- As per Tokyo guidelines, 4 components are given out of which presence of 1 will make diagnosis of moderate acute cholecystitis. 8 patients (23.53%) had WBC count more than 18000/mm³, 1 patient (2.94%) had a palpable mass in right upper quadrant, in 26 patients (76.47%) duration of complaints was more than 3 days, and local inflammatory changes were present in 14 patients (41.18%).

6. Severity of acute cholecystitis by age groups

Age groups	Mild	%	Moderate	%	Severe	%	Total	%
20-29yrs	6	60.00	2	20.00	2	20.00	10	9.09
30-39yrs	5	62.50	3	37.50	0	0.00	8	7.27
40-49yrs	12	63.16	5	26.32	2	10.53	19	17.27
50-59yrs	9	36.00	8	32.00	8	32.00	25	22.73
60-69yrs	12	38.71	10	32.26	9	29.03	31	28.18
>=70yrs	6	35.29	6	35.29	5	29.41	17	15.45
Total	50	45.45	34	30.91	26	23.64	110	100.00
Chi-square= 8.9257, p=0.1120								

Figure: Severity of acute cholecystitis by age groups



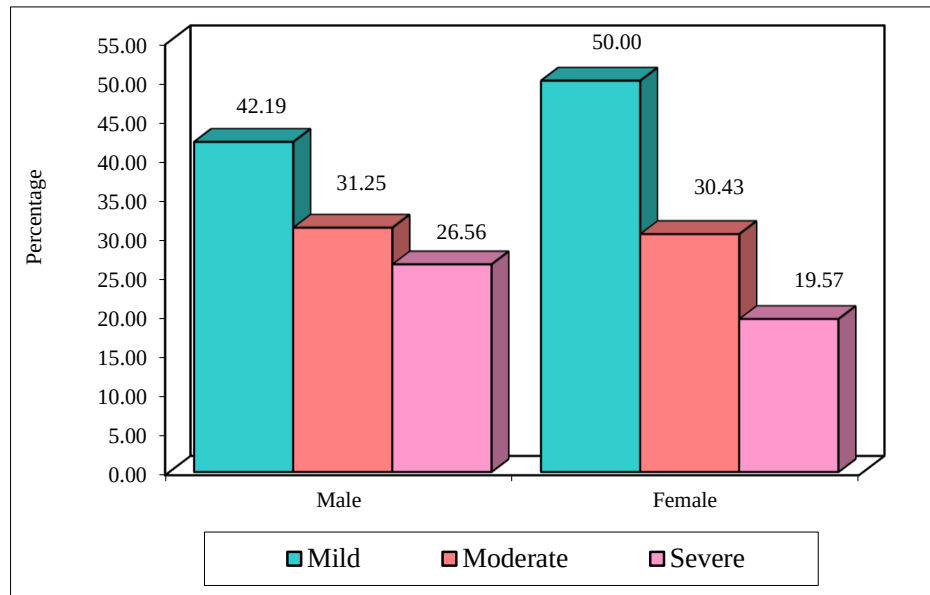
- In our study it is seen that cases of severe acute cholecystitis occurs more commonly after 50yrs of age.
- Percentage of Mild acute cholecystitis cases is higher in younger age group and percentage of severe acute cholecystitis goes on increasing as the age progresses.
- P value comparing severity of acute cholecystitis with age groups is 0.11 and is statistically insignificant. Mean age in this study came to be 54.9years.

7. Severity of acute cholecystitis by gender

Out of 110 patients , 64 (58.18%) were male and 46 (41.82%) were female.

Gender	Mild	%	Moderate	%	Severe	%	Total	%
Male	27	42.19	20	31.25	17	26.56	64	58.18
Female	23	50.00	14	30.43	9	19.57	46	41.82
Total	50	45.45	34	30.91	26	23.64	110	100.00
Chi-square= 0.9195,p=0.6314								

Figure: Severity of acute cholecystitis by gender

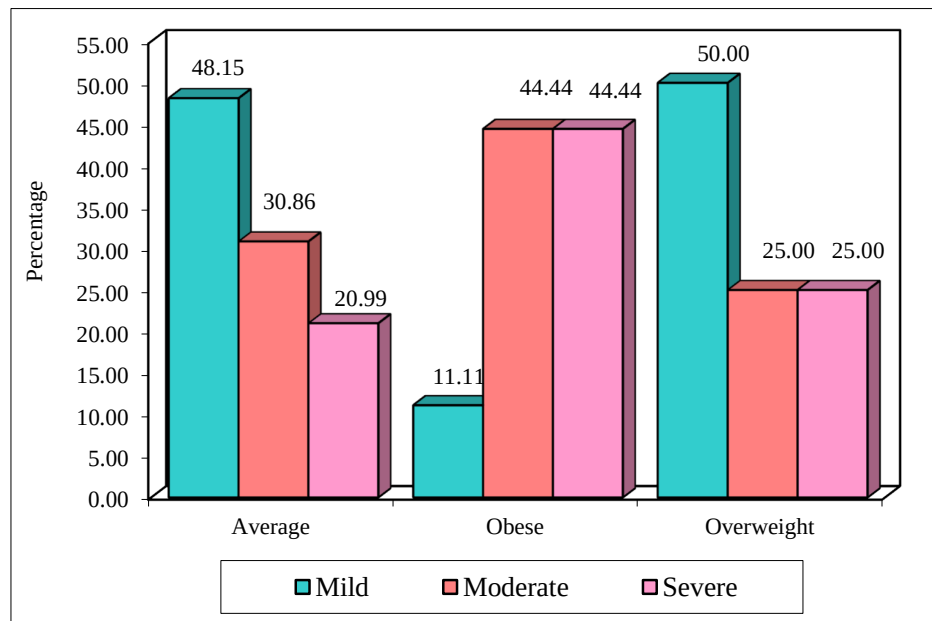


8. Severity of acute cholecystitis by status of built

Built	Mild	%	Moderate	%	Severe	%	Total	%
Average	39	48.15	25	30.86	17	20.99	81	73.64
Obese	1	11.11	4	44.44	4	44.44	9	8.18
Overweight	10	50.00	5	25.00	5	25.00	20	18.18
Total	50	45.45	34	30.91	26	23.64	110	100.00
Chi-square= 5.2198, p=0.2654								

Out of total 110 patients, 81 were average in built , 9 were obese and 20 were overweight. P value for comparison of built with severity of cholecystitis is 0.2 which is statistically insignificant.

Figure: Severity of acute cholecystitis by status of built



9. Comparison of Severity of acute cholecystitis with mean age, hospital stay (in days) and ICU stay (in days) by one way ANOVA

Parameter	Summary	Severity of acute cholecystitis				F-value	p-value	Pair wise comparisons		
		Mild	Moderate	Severe	Total			Mild vs mod	Mild vs severe	Mod vs severe
Age	Min	20.0	27.0	22.0	20.0	2.3152	0.1037	p=0.4357	p=0.0957	p=0.6470
	Max	77.0	94.0	83.0	94.0					
	Mean	51.8	56.0	59.5	54.9					
	SD	15.3	15.6	14.3	15.4					
Hospital stay (in days)	Min	3.0	4.0	7.0	3.0	62.3916	0.0001*	p=0.0001*	p=0.0001*	p=0.0001*
	Max	6.0	14.0	20.0	20.0					
	Mean	5.0	8.1	10.6	7.3					
	SD	0.8	2.6	3.1	3.1					
ICU stay (in days)	Min	0.0	0.0	2.0	0	117.2175	0.0001*	p=0.0001*	p=0.0001*	p=0.0001*
	Max	0.0	9.0	12.0	12.0					
	Mean	0.0	3.5	5.9	2.5					
	SD	0.0	2.4	2.1	2.9					

*p<0.05

- Mean hospital stay of patients with mild, moderate and severe cholecystitis is 5 days, 8.1 days and 10.6 days respectively. P value is 0.0001 which is statistically significant.

- Moderate acute cholecystitis patients had mean ICU stay for 3.5 days and severe acute cholecystitis patients had mean stay of 5.9 days.

P value is 0.0001 which is statistically significant.

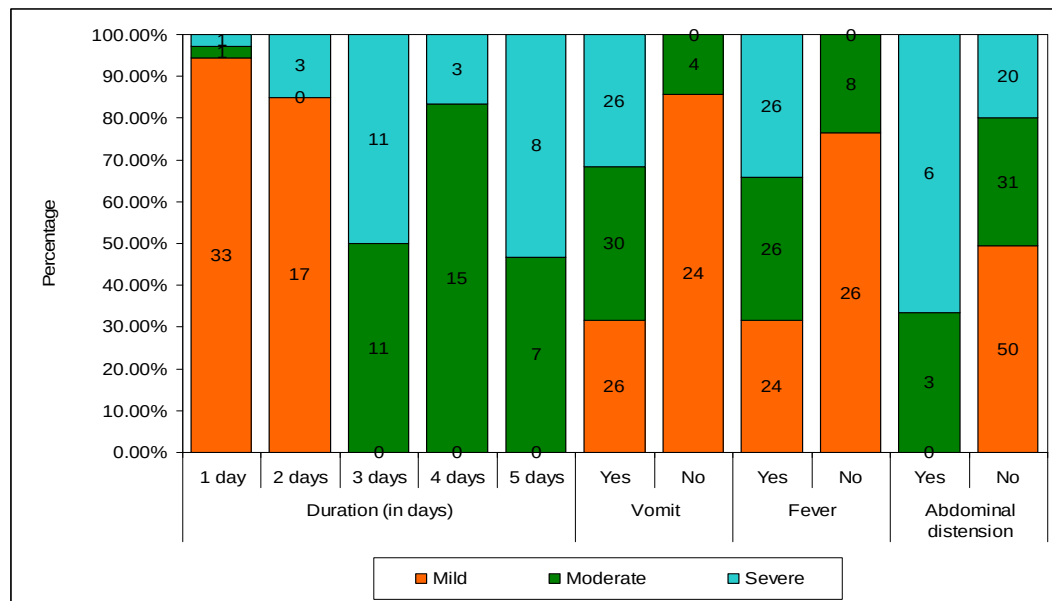
10. Comparison of Severity of acute cholecystitis with history of present illness

35 patients (31.82%) presented within 1 day of presentation of symptoms. Pain in abdomen, fever, vomiting were most common symptoms seen in severe cholecystitis.

Present illness	Mild	%	Moderate	%	Severe	%	Total	%	Chi-square	p-value
Pain										
Yes	50	45.45	34	30.91	26	23.64	110	100.0	-	-
No	0	0.00	0	0.00	0	0.00	0	0.00		
Duration (in days)										
1 day	33	94.29	1	2.86	1	2.86	35	31.82	104.598	0.0001*
2 days	17	85.00	0	0.00	3	15.00	20	18.18		
3 days	0	0.00	11	50.00	11	50.00	22	20.00		
4 days	0	0.00	15	83.33	3	16.67	18	16.36		
5 days	0	0.00	7	46.67	8	53.33	15	13.64		
Nausea										
Yes	50	45.45	34	30.91	26	23.64	110	100.0	-	-
No	0	0.00	0	0.00	0	0.00	0	0.00		
Vomit										
Yes	26	31.71	30	36.59	26	31.71	82	74.55	25.6300	0.0001*
No	24	85.71	4	14.29	0	0.00	28	25.45		
Fever										
Yes	24	31.58	26	34.21	26	34.21	76	69.09	22.9130	0.0001*
No	26	76.47	8	23.53	0	0.00	34	30.91		
Abdominal distension										
Yes	0	0.00	3	33.33	6	66.67	9	8.18	12.1530	0.0020*
No	50	49.50	31	30.69	20	19.80	101	91.82		
Total	50	45.45	34	30.91	26	23.64	110	100.0		

*p<0.05

Figure: Comparison of Severity of acute cholecystitis with history of present illness



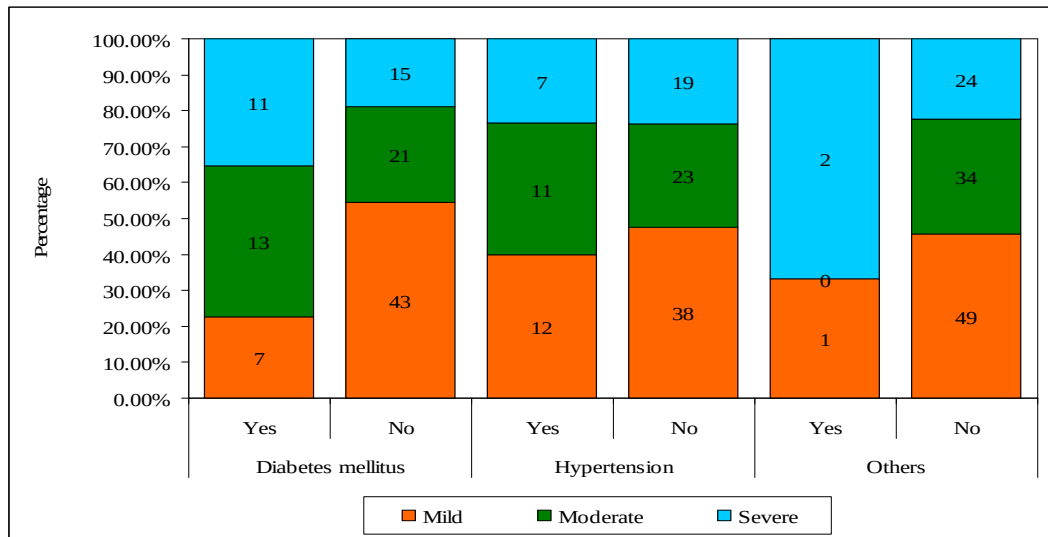
11. Comparison of Severity of acute cholecystitis with comorbidities

- Diabetes mellitus was present in 31 patients (28.18), it was associated with severity of cholecystitis with p value of 0.01 , which is statistically significant.

Comorbidities	Mild	%	Moderate	%	Severe	%	Total	%	Chi-square	p-value
Diabetes mellitus										
Yes	7	22.58	13	41.94	11	35.48	31	28.18	9.2300	0.0100*
No	43	54.43	21	26.58	15	18.99	79	71.82		
Hypertension										
Yes	12	40.00	11	36.67	7	23.33	30	27.27	0.7140	0.7000
No	38	47.50	23	28.75	19	23.75	80	72.73		

*p<0.05

Figure: Comparison of Severity of acute cholecystitis with comorbidities

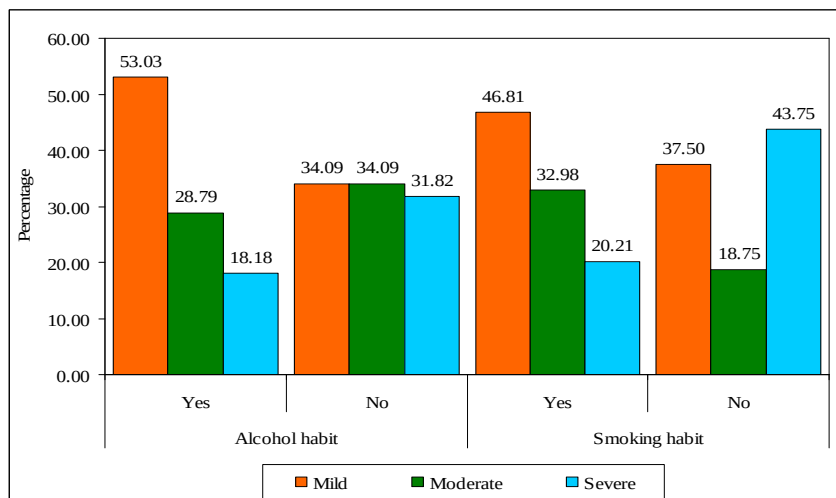


12. Comparison of Severity of acute cholecystitis with habits

Habits	Mild	%	Mode rate	%	Severe	%	Total	%	Chi-square	p-value
Alcohol habit										
Yes	35	53.03	19	28.79	12	18.18	66	60.00	4.4000	0.1110
No	15	34.09	15	34.09	14	31.82	44	40.00		
Smoking habit										
Yes	44	46.81	31	32.98	19	20.21	94	85.45	4.3610	0.1130
No	6	37.50	3	18.75	7	43.75	16	14.55		
Total	50	45.45	34	30.91	26	23.64	110	100.0		

No association was noted between habits and presence of acute cholecystitis.

Figure: Comparison of Severity of acute cholecystitis with habits



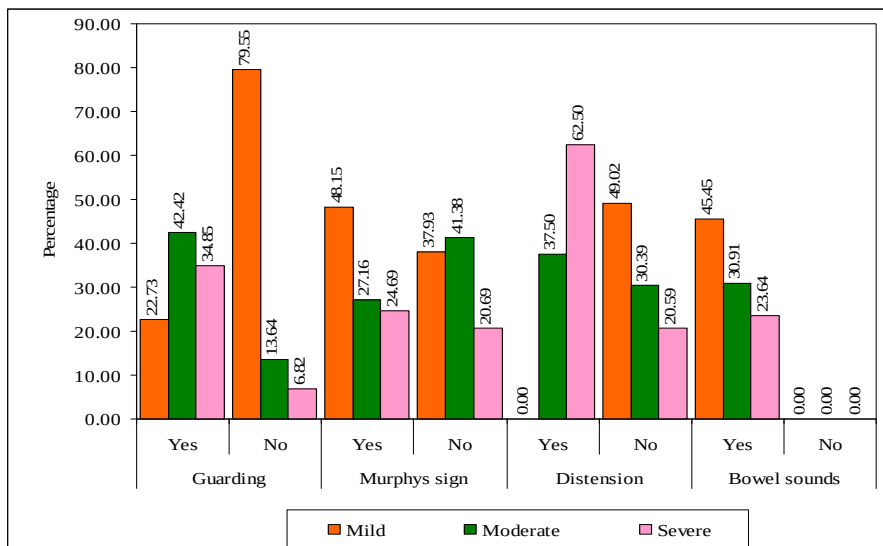
13. Comparison of Severity of acute cholecystitis with systemic examinations

Systemic examinations	Mild	%	Moderate rate	%	Severe	%	Total	%	Chi-square	p-value
Guarding										
Yes	15	22.73	28	42.42	23	34.85	66	60.00	34.6040	0.0001*
No	35	79.55	6	13.64	3	6.82	44	40.00		
Murphy's sign										
Yes	39	48.15	22	27.16	20	24.69	81	73.64	2.0320	0.3620
No	11	37.93	12	41.38	6	20.69	29	26.36		
Distension										
Yes	0	0.00	3	37.50	5	62.50	8	7.27	9.5560	0.0080*
No	50	49.02	31	30.39	21	20.59	102	92.73		
Bowel sounds										
Yes	50	45.45	34	30.91	26	23.64	110	100.0	-	-
No	0	0.00	0	0.00	0	0.00	0	0.00		
Total	50	45.45	34	30.91	26	23.64	110	100.0		

*p<0.05

- As per our study, guarding and distension of abdomen can differentiate between mild and severe acute cholecystitis since p value is <0.05.
- Murphy's sign is common in all grades and hence will not help to differentiate between mild and severe cases clinically.

Figure: Comparison of Severity of acute cholecystitis with systemic examinations

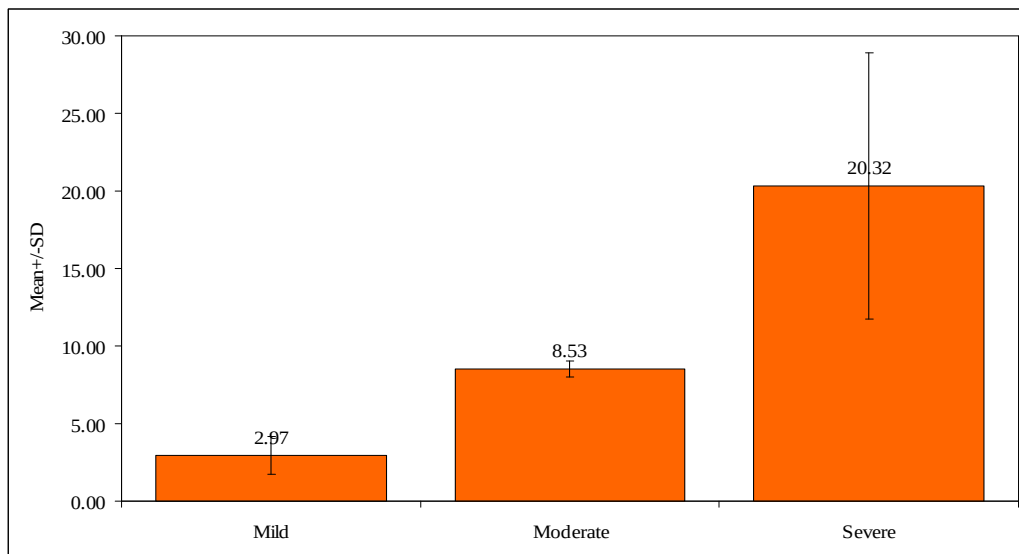


14. Comparison of Severity of acute cholecystitis with mean NLR by one way ANOVA

Summary	Severity of acute cholecystitis				F-value	p-value	Pair wise comparisons		
	Mild	Moderate	Severe	Total			Mild vs mod	Mild vs sev	Mod vs sev
Min	1.20	7.45	10.00	1.20	142.1394	0.0001*	p=0.0001*	p=0.0001*	p=0.0001*
Max	6.50	9.50	46.00	46.00					
Mean	2.97	8.53	20.32	8.78					
SD	1.22	0.49	8.62	8.07					

- Neutrophil lymphocyte ratio can be used as a marker for severe acute cholecystitis based on findings of our study.
- NLR 1.2 – 6.5 can be taken as mild acute cholecystitis. NLR 6.5 to 9.5 can be taken as moderate cholecystitis. NLR >10 can be taken as severe acute cholecystitis

Figure: Comparison of Severity of acute cholecystitis with mean NLR by one way ANOVA



15. Comparison of Severity of acute cholecystitis with various investigations by one way ANOVA

Investigations	Severity of acute cholecystitis								p-value	Pair wise comparisons			
	Mild		Moderate		Severe		Total						
	Mean	SD	Mean	SD	Mean	SD	Mean	SD			Mild vs mod	Mild vs sev	Mod vs sev
HB	12.64	1.93	12.58	1.55	11.52	2.22	12.36	1.93	0.0407*	0.9910	0.0440	0.0860	
TLC	10374.2	2394.84	17144.4	3369.6	18976.9	6641.1	14500.18	5558.97	0.0001*	0.0001*	0.0001*	0.1970	
PLT	289360.0	77942.6	274676.4	89210.2	215538.4	103549.1	267372.7	92081.4	0.0029*	0.7340	0.0020*	0.0300*	
RBC	4.41	0.51	4.58	0.51	4.45	0.63	4.47	0.54	0.3503	0.3240	0.9380	0.6340	
TBILI	0.87	0.58	1.09	0.78	2.43	3.65	1.31	1.95	0.0026*	0.8640	0.0020*	0.0180*	
D BILI	0.41	0.41	0.63	0.60	1.71	3.33	0.79	1.73	0.0058*	0.8300	0.0050*	0.0370*	
SGOT	30.96	23.24	34.09	19.94	42.15	31.31	34.57	24.65	0.1705	0.8340	0.1460	0.4180	
SGPT	31.62	23.54	45.91	48.87	41.08	39.18	38.27	36.94	0.2005	0.1910	0.5380	0.8690	
ALP	100.02	106.18	126.32	129.35	123.54	92.33	113.71	110.67	0.4978	0.5370	0.6560	0.9950	
TP	6.65	0.52	6.64	0.72	6.12	0.89	6.52	0.72	0.0036*	0.9980	0.0050*	0.0110*	
S. ALB	3.61	0.50	3.59	0.55	3.27	0.72	3.52	0.59	0.0442*	0.9870	0.0470*	0.0940	
A:G	1.20	0.27	1.14	0.26	1.22	0.40	1.19	0.30	0.6192	0.7080	0.9690	0.6410	
PT	12.38	1.21	12.49	1.45	13.38	3.13	12.65	1.92	0.0824	0.9590	0.0780	0.1770	
INR	1.13	0.16	1.19	0.18	1.33	0.29	1.20	0.22	0.0004*	0.4240	0.0001*	0.0180*	
RBS	112.72	16.69	120.71	23.33	118.20	39.27	116.48	25.62	0.3498	0.3430	0.6510	0.9250	
HbA1c	6.75	0.38	7.33	1.29	8.85	2.71	7.88	2.09	0.1994	0.8950	0.2330	0.3650	
S. AMYLASE	27.34	10.50	31.36	22.17	29.50	14.32	29.07	15.69	0.5178	0.4920	0.8380	0.8940	
S. LIPASE	26.02	8.42	27.45	13.91	28.62	7.90	27.07	10.25	0.5637	0.8090	0.5520	0.9030	
HSCRP	30.93	16.59	144.50	55.92	327.38	115.89	136.10	134.07	0.0001*	0.0001*	0.0001*	0.0001*	
UREA	19.06	8.11	24.47	11.30	64.42	36.47	31.45	26.80	0.0001*	0.4280	0.0001*	0.0001*	
CREAT	0.84	0.25	0.93	0.25	2.07	0.97	1.16	0.72	0.0001*	0.7140	0.0001*	0.0001*	
NA	136.58	3.46	134.82	8.51	131.23	8.11	134.77	6.85	0.0046*	0.4540	0.0030*	0.0950	
K	4.10	0.39	4.18	0.52	4.23	0.77	4.15	0.54	0.5786	0.7590	0.5900	0.9500	
CL	101.81	3.76	96.55	15.58	97.81	8.52	99.24	10.02	0.0500*	0.0260*	0.4380	0.5110	
HCO3	20.30	2.60	20.09	3.51	17.50	2.87	19.57	3.17	0.0004*	0.9480	0.0001*	0.0030*	

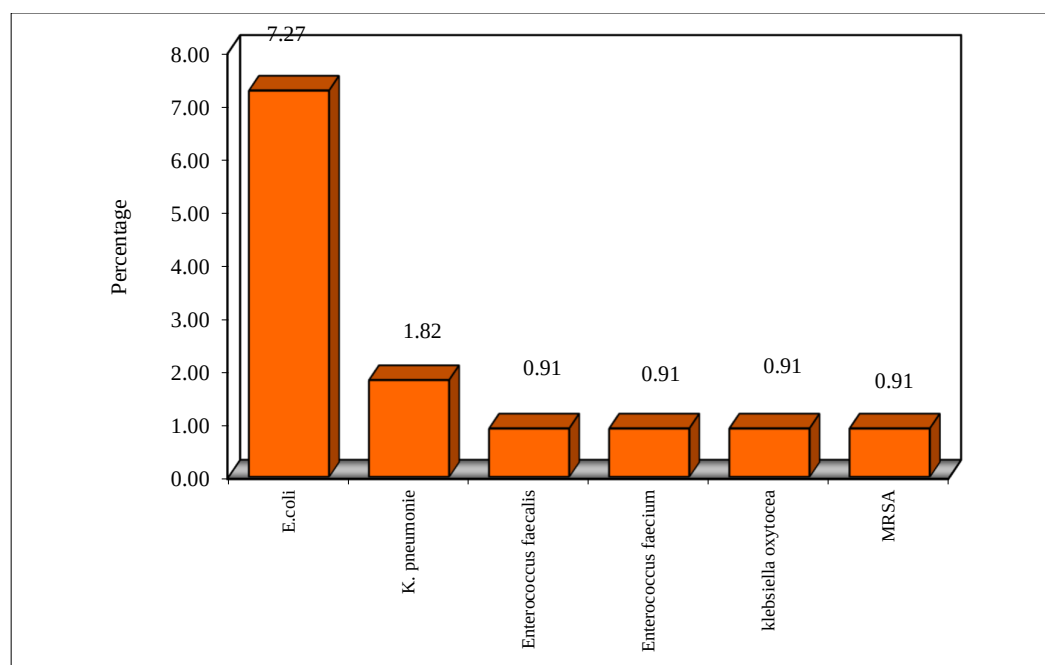
Total proteins, Serum albumin, Hscrp values were shown to be statistically significant to differentiate between mild and severe cholecystitis

16. Comparison of Severity of acute cholecystitis with Drain fluid(Cholecystostomy) Culture Sensitivity:

C/S	Number	%
E.coli	8	7.27
Klebsiella pneumonie	2	1.82
Enterococcus faecalis	1	0.91
Enterococcus faecium	1	0.91
Klebsiella oxytocea	1	0.91
MRSA	1	0.91

- 8 patients showed presence of E. coli in their culture report followed by Klebsiella pneumonie in 2 patients.

Figure: Bar diagram showing organisms isolated in culture sensitivity of cholecystostomy drain fluid

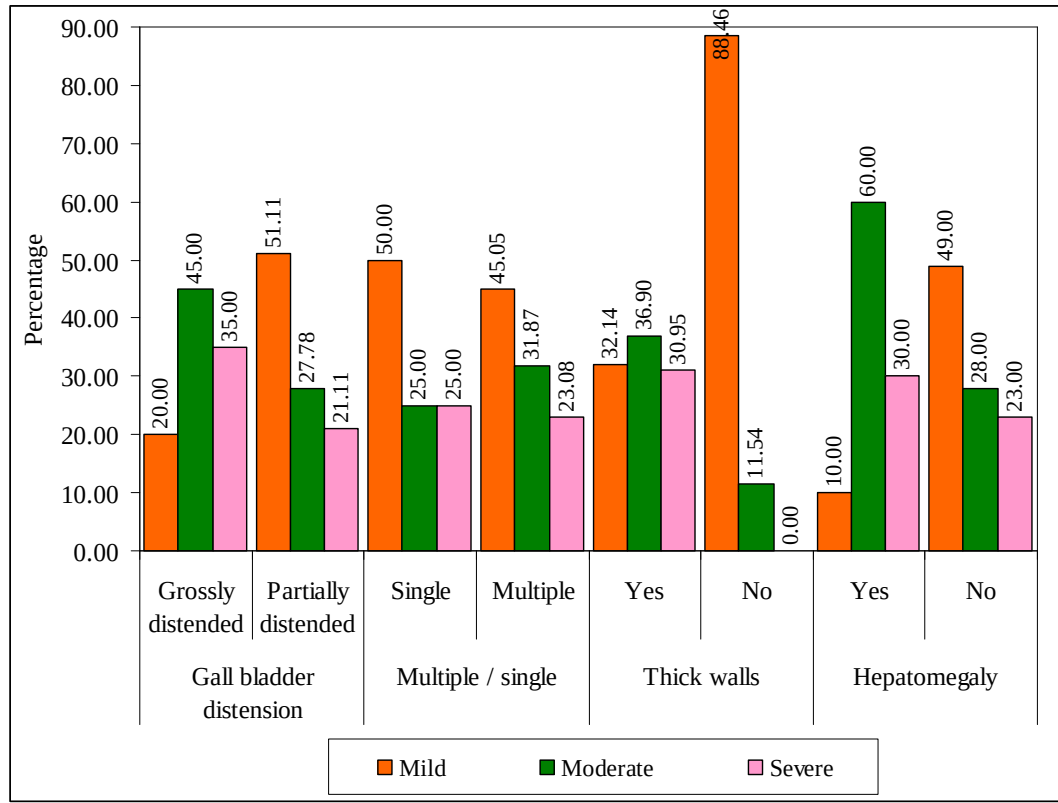


17. Comparison of Severity of acute cholecystitis with USG findings

USG findings	Mild	%	Mode rate	%	Severe	%	Total	%	Chi-square	p-value
Gall bladder distension										
Grossly distended	4	20.00	9	45.00	7	35.00	20	18.18	6.3902	0.0409*
Partially distended	46	51.11	25	27.78	19	21.11	90	81.82		
Multiple / single										
Single	8	50.00	4	25.00	4	25.00	16	14.55	0.5304	0.9704
Multiple	41	45.05	29	31.87	21	23.08	91	82.73		
Nil	1	33.33	1	33.33	1	33.33	3	2.73		
Thick walls										
Yes	27	32.14	31	36.90	26	30.95	84	76.36	26.0352	0.0001*
No	23	88.46	3	11.54	0	0.00	26	23.64		
Hepatomegaly										
Yes	1	10.00	6	60.00	3	30.00	10	9.09	6.2422	0.0441*
No	49	49.00	28	28.00	23	23.00	100	90.91		
Total	50	45.45	34	30.91	26	23.64	110	100.0		

*p<0.05

Figure: Comparison of Severity of acute cholecystitis with USG findings



- Gall bladder was grossly distended in 20 patients and partially distended in 90 patients.
- Multiple gallbladder calculi were seen in 91 patients and single gallstone was detected in 16 patients on ultrasonography.
- Thick gallbladder wall was present in 84 patients.
- Associated finding of hepatomegaly was present in 10 patients.

18. Comparison of Severity of acute cholecystitis with various USG findings by one way ANOVA: gall stones and GB wall thickness

USG findings	Severity of acute cholecystitis								p-value	Pair wise comparisons		
	Mild		Moderate		Severe		Total			Mild vs mod	Mild vs sev	Mod vs sev
	Mean	SD	Mean	SD	Mean	SD	Mean	SD				
Area of stone	86.96	69.79	80.71	94.69	137.78	147.87	96.58	100.79	0.0796	0.9601	0.1114	0.1004
Thickness (MM)	3.88	1.58	5.43	1.54	6.32	1.29	4.98	1.80	0.0001*	0.0001*	0.0001*	0.0668

*p<0.05

- In Ultrasonography findings , thickness of gallbladder wall is important factor to differentiate between mild and severe cholecystitis. However , it cannot differentiate between moderate and severe cholecystitis.
- Mean thickness of gallbladder wall was 3.88 in mild cholecystitis , 5.43mm in moderate cholecystitis and 6.32mm in severe cholecystitis.

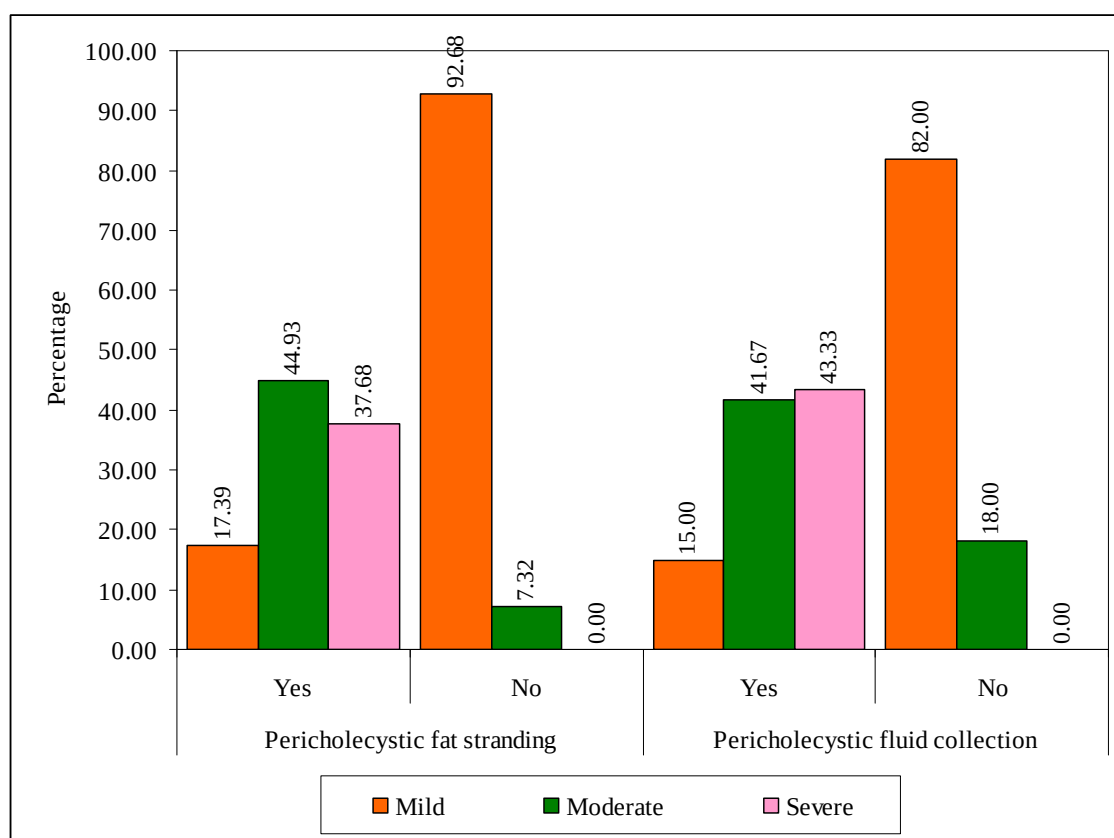
19. Comparison of Severity of acute cholecystitis with pericholecystic findings

Pericholecystic findings	Mild	%	Moderate	%	Severe	%	Total	%	Chi-square	p-value
Pericholecystic fat stranding										
Yes	12	17.39	31	44.93	26	37.68	69	62.73	59.2934	0.0001*
No	38	92.68	3	7.32	0	0.00	41	37.27		
Pericholecystic fluid collection										
Yes	9	15.00	25	41.67	26	43.33	60	54.55	53.5426	0.0001*
No	41	82.00	9	18.00	0	0.00	50	45.45		
Total	50	45.45	34	30.91	26	23.64	110	100.00		

*p<0.05

- Pericholecystic fat stranding was seen in 17.39% cases on mild cholecystitis , 44.93% of moderate cholecystitis and 37.68% of severe cholecystitis.
- Pericholecystic fluid collection was seen in 15% of mild cholecystitis , 41.67% of moderate cholecystitis and 43.33% of severe cholecystitis.

Figure: Comparison of Severity of acute cholecystitis with pericholecystic findings



20. Comparison of Severity of acute cholecystitis with treatment modalities :

Treatment Modalities	Mild	%	Moderate	%	Severe	%	Total	%
Treatment								
Percutaneous drainage	0	0.00	5	41.67	7	58.33	12	10.91
Surgery done								
Laparoscopic cholecystectomy	20	76.92	5	19.23	1	3.85	26	23.64
Laparoscopic subtotal cholecystectomy	0	0.00	2	100.00	0	0.00	2	1.82
Laparoscopic to open converted cholecystectomy	0	0.00	1	50.00	1	50.00	2	1.82

*p<0.05

- Percutaneous drainage of distended gallbladder was done in 12 patients out of which 5 had moderate cholecystitis and 7 had severe cholecystitis.
- Laparoscopic total cholecystectomy was done in 20 mild cholecystitis patients, 5 moderate cholecystitis and 1 severe cholecystitis patient.
- Laparoscopic subtotal cholecystectomy was done in 2 moderate cholecystitis patients due to dense adhesions.
- 2 cases were converted to open surgery, one belonging to moderate cholecystitis and 1 belonging to severe cholecystitis group.

21. Sensitivity, Specificity and cut off point for NLR values in prediction of Severity of acute cholecystitis

Summary	Severe by (mild + moderate)	Severe by mild	Severe by moderate
Cut-off point	≥ 13.00	≥ 9.20	≥ 13.00
AUC	0.9725	0.9800	0.9615
Specificity	0.8846	1.0000	0.8846
Sensitivity	0.9762	0.9800	0.9706
Positive predictive value	0.9200	0.9630	0.9583
Correctly classified	0.9545	0.9868	0.9333

NLR can differentiate between mild and severe cholecystitis with sensitivity of 98% and specificity of 100% , and between moderate and severe cholecystitis with sensitivity of 97% and specificity of 88%.

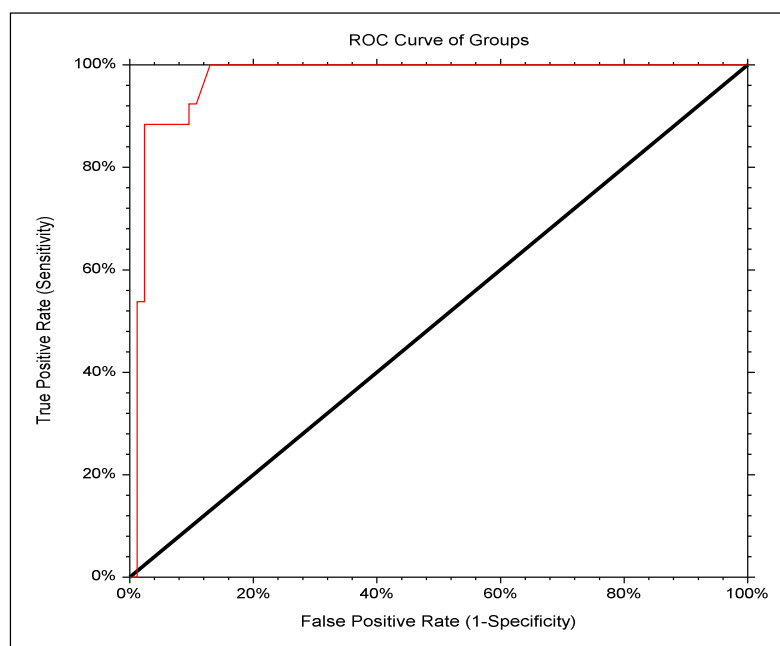
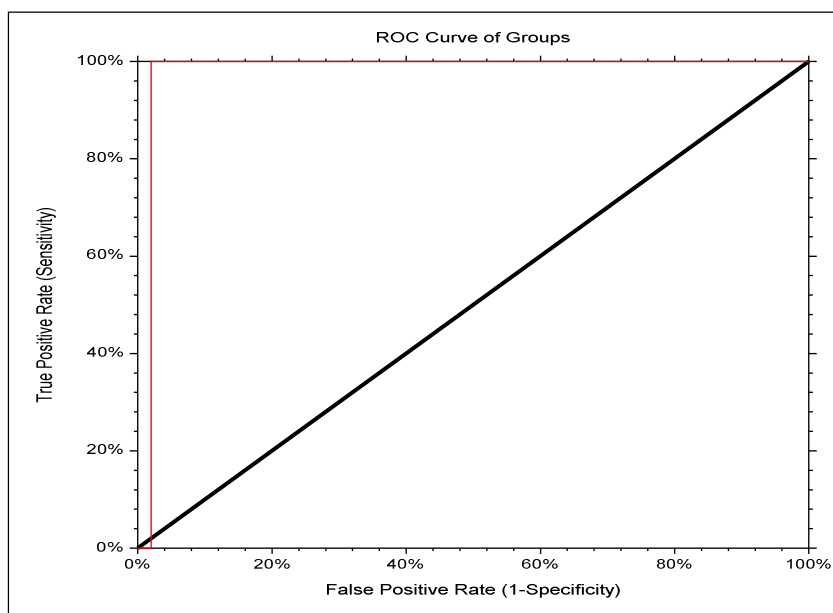
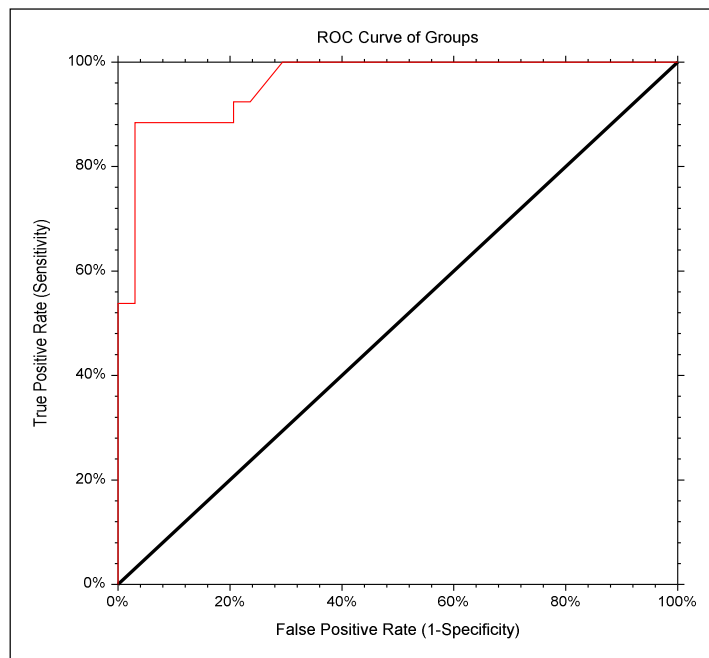
Figure: ROC - Severe by mild + moderate**Figure: ROC - Severe by mild**

Figure: ROC - Severe by moderate

DISCUSSION

The general prevalence of gall bladder calculi varies between 10%-15% of the general population. Acute cholecystitis occurs with an annual incidence of 1% -3%²⁰. The aim of this study was for prediction of cholecystitis severity so that it guides early detection with prompt and efficient management of both local and systemic complications.

In a developing country like India, a simple, cost effective, non-invasive yet accurate method of prediction becomes the need of the hour. This method may also be utilised by our healthcare workers in the rural set up as well as tertiary care centres for managing patients effectively²³. For prediction of severe cholecystitis, several biochemical markers have been suggested however NLR is preferred because it is inexpensive and easy to calculate from standard blood counts. Platelet lymphocyte ratio, immature granulocyte counts are some other parameters which were studied for prognosis of acute cholecystitis but Neutrophil to lymphocyte ratio is proven to be better marker as per studies conducted by Korkut et al²⁵ and Bedel et al²⁶.

The inflammation of gallbladder usually triggers the release of arachidonic acid metabolites and platelet-activating factors which results in neutrophilia. Simultaneously cortisol-induced stress results in relative lymphopenia, and thus, the NLR accurately represents the ongoing inflammatory process.

Our study was a prospective observational study carried out 110 patients who were admitted with diagnosis of acute cholecystitis from emergency department and outpatient department of Department of General surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum from January 2021 to December 2021. All patients who fulfilled the inclusion criteria and were willing to participate were included in the study.

In our study, mean age of patient was 54.9 years(22 – 94years). Incidence of acute cholecystitis was seen to be increasing after 50 years age. 84% patients having severe cholecystitis had age >50years. Thus, severity of cholecystitis is seen to be increasing with age. Similar finding of increased incidence of acute cholecystitis with age has was shown by study conducted by Yasar et al²⁰ and Lee et al¹. In people with age group more than 60 years, severe cholecystitis can develop into multiple organ dysfunction syndrome compared with mild AC. Therefore, it is essential to take active steps for appropriate treatment based on severity of acute cholecystitis.

Out of 110 patients, 64 (58.18%) were male and 46 (41.82%) were female. No significant association seen between gender and acute cholecystitis.

Majority of patients presented with complaints of abdominal pain, nausea, vomiting, abdominal distension and fever. 94% of mild cholecystitis cases presented on day 1 of onset of complaints whereas around 50% of severe acute cholecystitis patients presented on or after third day after onset of symptoms. Diabetes mellitus was a comorbidity amongst 31% patients and it was seen to be related in deciding severity of cholecystitis with $p < 0.05$.

As per Tokyo guidelines, out of total 110 patients, 23.64% had severe acute cholecystitis, 30.91% had moderate and 45.45% had mild cholecystitis. A total of 3(2.73%) patients had acute acalculous cholecystitis and rest were cases of calculous cholecystitis (97.27%).

In our study, it was seen that Neutrophil lymphocyte ratio at admission could be used as a potential prognostic marker for severe acute cholecystitis. It was practically observed that patients with Mild acute cholecystitis as per Tokyo guidelines, had NLR ranging from 1.2 – 6.5. Patients with moderate cholecystitis had NLR ranging between 6.5 to 10. The patients diagnosed with severe acute

cholecystitis as per Tokyo guidelines had $\text{NLR} > 10$. In the study conducted by SH Woo², the NLR cut off value of 9.9 (OR, 4.20; 95% CI, 1.01–17.53; $P = 0.049$) was an independent predictive factor for severe AC in elderly patients in the Emergency department. Our study findings are consistent with this study.

67.27% patients of acute cholecystitis have shown increased total leucocyte count. Mean TLC for mild cholecystitis is 10374 ± 2394 , moderate is 17144 ± 3369 and severe cholecystitis is 18976 ± 6641.1 . Thus, it was seen that TLC is not raised in all cases of acute cholecystitis and hence cannot be used as potential biomarker for diagnosis or for grading acute cholecystitis. Other blood parameters which were seen to change with severity of cholecystitis: serum protein, serum albumin were seen to have lower values and PT/INR, hsCRP were significantly higher in severe group as compared to the mild cholecystitis group ($P < 0.001$). However, these parameters couldn't differentiate between moderate and severe cholecystitis groups.

Diagnosis of severe cholecystitis was made based on Tokyo guidelines as per which cardiovascular system was seen to be most commonly affected in 65.38% followed by renal parameter derangement in 42.31%.

Complicated gall bladder disease was seen in both moderate and severe groups of acute cholecystitis. Gallbladder perforation was the commonest complication accounting to 55.17%. Empyema gall bladder amounted to 20.68% of complications followed by acute emphysematous cholecystitis (13.7%) and then acute gangrenous cholecystitis (10.3%).

It was found in our study that mean hospital stay and Intensive care unit stay was more with patients having severe acute cholecystitis. Mean hospital stay of patients with mild, moderate and severe cholecystitis is 5 days, 8.1 days and 10.6 days respectively. Moderate acute cholecystitis patients had mean ICU stay for 3.5 days

and severe acute cholecystitis patients had mean stay of 5.9 days. P value is 0.0001 which is statistically significant. As per study conducted by SH Woo et al², median hospital stay was 11 days in the severe group and 6 days in the nonsevere group ($P < 0.001$), which is consistent with our findings. Thus, Neutrophil lymphocyte ratio which helps to recognize patients at risk of severe cholecystitis can help to assess number of hospital and ICU days which could be required for patients at presentation which can facilitate better patient counselling at the time of admission.

Radiological investigations of Ultrasonography and CT scan have known to help in diagnosis of Acute cholecystitis. In our study, pericholecystic fat stranding was seen in 17.39% cases on mild cholecystitis, 44.93% of moderate cholecystitis and 37.68% of severe cholecystitis. Pericholecystic fluid collection was seen in 15% of mild cholecystitis, 41.67% of moderate cholecystitis and 43.33% of severe cholecystitis. Thick gallbladder wall ($>4\text{mm}$) was present in 84 patients. In Ultrasonography findings, thickness of gallbladder wall, pericholecystic fat stranding and pericholecystic fluid collection were important factors to differentiate between mild and severe cholecystitis. These CT and USG findings help to diagnose severe cholecystitis but cannot differentiate between moderate and severe acute cholecystitis. A study by Swathi et al²⁷ showed that gall bladder wall thickening was found to be higher in severe cholecystitis cases as compared to simple cholecystitis cases and this was found to be statistically significant at p value <0.001 . Wall thickness of 4mm was predominantly seen in severe cholecystitis cases which was similar to our study.

Based on treatment given to patients, percutaneous drainage of distended gallbladder was done in 12 patients out of which 5 had moderate cholecystitis and 7 had severe cholecystitis. Laparoscopic total cholecystectomy was done in 20 mild cholecystitis patients, 5 moderate cholecystitis and 1 severe cholecystitis patient.

Laparoscopic subtotal cholecystectomy was done in 2 moderate cholecystitis patients due to dense adhesions. 2 cases were converted to open surgery, one belonging to moderate cholecystitis and 1 belonging to severe cholecystitis group.

In all patients who underwent cholecystostomy, drain fluid was sent for culture sensitivity and it was seen that 8 patients showed presence of *E. coli* in their culture report followed by *klebsiella pneumoniae* in 2 patients.

In a study carried out by Mahmood²², results showed that the patient's age (OR=1.047; $p=0.003$), higher CRP (OR=1.005; $p=0.012$) and NLR (OR=1.094; $p=0.047$) were significant independent factors associated with severity of cholecystitis. The median post-operative length of stay was four days. CT is more useful for identifying complications, such as emphysematous cholecystitis and GB perforation, than for diagnosing AC or differentiating AC from other diseases with similar symptoms.

As per Vela Ponanco²⁸, NLR cut-off of 12.48 was able to predict severe AC with 70% sensitivity and 70% specificity. A NLR value of 12.48 was significantly associated with older age ($p<0.001$), severe AC ($p<0.001$), lesser cholecystectomies ($p<0.001$), more cholecystostomies ($p<0.001$), higher grades of complications ($p<0.05$), prolonged hospital-stay ($p<0.05$) and higher mortality ($p<0.05$).

CONCLUSION

Preoperative Neutrophil to lymphocyte ratio calculation is an inexpensive and reliable test that can give insight about severity of cholecystitis and can predict prognosis at time of admission. According to results found in this study, the patients admitted with acute cholecystitis can be considered to have mild cholecystitis if NLR at admission is < 6.5 , moderate cholecystitis if it is between 6.5 to 10 and severe cholecystitis if NLR at admission is > 10 . Our results substantiate that Neutrophil Lymphocyte Ratio can be used as a prognostic marker in assessing, managing and prioritizing patients of acute cholecystitis.

As per Neutrophil lymphocyte ratio of patient, decision can be taken to see if patient can be managed conservatively or should be taken for laparoscopic cholecystectomy or to plan percutaneous cholecystostomy to decompress gall bladder and relieve complications due to sepsis.

SUMMARY

Acute cholecystitis is defined as the inflammation of the gall bladder occurring due to cystic duct obstruction from stones, sludge leading to bile stasis and subsequent mechanical, chemical or infectious irritation of the gall bladder wall. Increased morbidity results from delayed identification and treatment of acute cholecystitis because it progresses to severe cholecystitis, such as hemorrhage, empyema, gangrene, perforation of gallbladder, adhesions, challenging dissection of Calot's triangle, emphysema or when the pathological examination indicated xanthogranulomatous cholecystitis. It is challenging to diagnose severe cholecystitis both clinically and radiologically. Patients with uncomplicated acute cholecystitis and those with severe acute cholecystitis have significantly different morbidity and death rates. Therefore, it is essential to properly diagnose and treat patients who are at risk of developing severe cholecystitis in order to avoid any related consequences.

It was seen in our study that NLR can be used for prioritization of patients for admissions. NLR value less than 6.5 is suggestive of mild cholecystitis, between 6.5 to 10 is moderate cholecystitis and more than 10 is severe cholecystitis. Based on mild, moderate and severe grading as per Neutrophil lymphocyte ratio, decision can be made whether patient can be treated on outpatient or inpatient basis. Patients with old age and who have diabetes as a comorbidity have higher risk to get severe acute cholecystitis for which they might need careful monitoring and ICU care. Patients more than 60 years age can develop into multiple organ dysfunction syndrome if not managed efficiently. Cardiovascular system is most commonly affected followed by renal parameters derangement.

Based on NLR at admission , patient and relatives can be explained about prognosis of patient and possible number of days of stay in hospital or ICU. It can help in better patient counselling at admission.

Plan of management of Acute cholecystitis can be made based on NLR value at admission. Patients who have low NLR less than 6.5 can be planned for laparoscopic cholecystectomy. Those with moderate cholecystitis can be either planned for cholecystectomy or could be managed conservatively. Patients who are diagnosed to progress to severe cholecystitis should be managed conservatively with Antibiotics and percutaneous cholecystostomy till septic features subside. This will reduce the rate of laparoscopic to open conversion of cholecystectomies.

SCOPE AND LIMITATIONS

Neutrophil lymphocyte ratio can be used for:

1. Prioritization of patients for admissions
2. >60 years - severe cholecystitis can develop into multiple organ dysfunction syndrome compared with mild AC.
3. ICU and hospital stay: Better preoperative counselling is possible
4. Plan of management: Conservative / Laparoscopic cholecystectomy /
Cholecystostomies: to lower laparoscopic to open conversion rates

LIMITATIONS

1. Small sample size
2. Single institute study

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ANNEXURE I : CONSENT

INFORMED CONSENT FOR PARTICIPATION IN RESEARCH STUDY

Mr./Miss /Mrs. _____ we are requesting you to enroll yourself in study titled **“A prospective study to evaluate use of Neutrophil to lymphocyte ratio (NLR) as a marker for severe acute cholecystitis. ”**, conducted by REG NO: BH0120010, Postgraduate in M.S.General Surgery under the guidance of Dr. _____, Associate Professor in Department of General Surgery, J.N. MEDICAL COLLEGE, Belagavi .

Respected Sir/ Madam,

We request you to kindly participate in our study. Your participation in the research is voluntary. Your decision to participate in the study or otherwise will not affect the relationship with KLES Dr. Prabhakar Kore hospital. If you decide not to participate, you are free to withdraw at any time.

Purpose of study:

The purpose of the study is to evaluate the utility of the NLR as a prognostic indicator in patients with acute cholecystitis, and to identify a relevant ratio value that discriminates between simple and severe acute cholecystitis.

Procedure :

If you agree to enroll yourself in this study, your detailed history will be taken and you will be clinically examined in detail. Investigations like Hemoglobin, WBC Total Count, Differential Count, CRP, LFT, RFT , CT Abdomen will be done and noted down.

Risks and Benefits:

There is no increased risk involved in being a part of this study and the complications are those which are normally anticipated. The results derived at the end of the study will possibly benefit all similar patients admitted in this hospital and elsewhere.

Type of Study : This study is an prospective observational study.

Participant selection

It includes all patients with acute cholecystitis, as per the exclusion and inclusion criteria.

Voluntary Participation

Your participation in research is voluntary. It is your choice whether to participate or not. Your decision whether to participate in the study or not will not change present or future health care services offered to you and will not affect your relationship with J.N. Medical College. If you choose not to participate in this study, you will still be offered the routine treatment that is given at our hospital. You will continue to receive the routine care at our hospital even if you decline to participate in this study. If you decide to participate you are free to withdraw at any time.

Privacy and Confidentiality:

The only people who will know that you are the research subject will be the members of the research team. No information about you or information provided by you during the research will be disclosed to others without your written permission except:

1. In emergency to protect your rights and welfare.
2. If required by law.

Authorization to Publish Results:

When the results of the research are published or discussed, in a conference, no information will be displayed that will disclose your identity. Any information that is obtained in connection with this study and that can be identified with you will remain confidential.

Right to refuse or withdraw from study:

You do not have to participate in this research if you do not wish to. You can withdraw at any time from the study. There will be no penalty for withdrawal. Your treatment and care in this hospital will not change irrespective of whether you agree to participate or not. You can be removed from the study if necessary.

Alternative:

You are free to withdraw yourself from this study at any point of time. You will continue to receive the routine care even if you decline to participate in the study. You will be treated for the same even if you have declined from the study. You will be informed about any new information that may affect your decision to participate in the study.

Institutional/sponsor's policy:

In the event of any injury related to the study, treatment will be made available through KLE's Hospital & MRC, Belgaum. There is no compensation or payment for such medical treatment by law. If you are injured you may contact REG NO: BH0120010, Post graduate student, Department of General Surgery, KLE's Hospital& MRC.

Consent statement

Mode of communication of consent form: Verbal / Written

Contents: Self read /Read out by Investigator

Participant's awareness regarding voluntary withdrawal from study: Yes / No

Investigators decision to remove participants from study: Yes / No

Awareness regarding voluntary participation: Yes/ No

Adequate time given to clarify any doubts about the study or rights to study participant:
Yes/ No

In case they have any questions related to the study, in future or in case of study related injury or illness, they can contact REG NO: BH0120010, Department of General Surgery, KLES Hospital and MRC, Belagavi, Phone number- _____ or Dr. _____, Associate Professor, Department of General Surgery, KLES Hospital and MRC, Belagavi.

If they have any queries about their rights as a study subject, they may call DR. ROOPA BELLAD M.D., Chairman, and Ethical Committee for Human Subjects Research, Professor, Department of Paediatrics, J. N. Medical College, Belagavi, Phone number- 9448113403.

Signature or left thumb print of participant or legally authorized representative

_____ Participant's name. _____ Participant's signature/thumb print

_____ Experimenters' name _____ Experimenters' signature

_____ Witness' name _____ Witness' signature

ANNEXURE II: PROFORMA

A prospective study to evaluate use of Neutrophil to lymphocyte ratio (NLR) as a marker for severe acute cholecystitis.

NAME :		
AGE :	SEX :	IP NUMBER :
ADDRESS :		
OCCUPATION		
ADMISSION :		DISCHARGE:
DURATION HOSPITAL :		ICU STAY :
HISTORY OF PRESENT ILLNESS :		
PAST HISTORY :		
PERSONAL HISTORY :		

GENERAL AND SYSTEMIC

EXAMINATION

HEIGHT:	WEIGHT :	BMI:
BUILT :	Pallor / icterus / lymphadenopathy /cyanosis/clubbing	

PULSE :	BP :
TEMP :	RR :

TABLE 67.1 Tokyo Consensus Guidelines for severity grading of acute cholecystitis. Reproduced with permission from Yokoe et al. *J Hepatobiliary Pancreat Sci* 2013; **30**: 35–46.

Grade III (severe) acute cholecystitis	
Associated with dysfunction of any one of the following organs/systems:	
1 Cardiovascular dysfunction	Hypertension requiring treatment with dopamine $\leq 5 \mu\text{g/kg/min}$, or any dose of norepinephrine (noradrenaline)
2 Neurological dysfunction	Decreased level of consciousness
3 Respiratory dysfunction	P_aO_2/FiO_2 ratio < 300
4 Renal dysfunction	Oliguria; creatinine $> 2.0 \text{ mg/dL}$
5 Hepatic dysfunction	Prothrombin time (PT-INR) > 1.5
6 Haematological dysfunction	Platelet count $< 100\,000/\text{mm}^3$
Grade II (moderate) acute cholecystitis	
Associated with any one of the following conditions:	
1 Elevated white cell count ($> 18\,000/\text{mm}^3$)	
2 Palpable tender mass in the right upper abdominal quadrant	
3 Duration of complaints > 72 hours	
4 Marked local inflammation (gangrenous cholecystitis, pericholecystic abscess, hepatic abscess, biliary peritonitis, emphysematous cholecystitis)	
Grade I (mild) acute cholecystitis	
Does not meet the criteria of grade II or grade III acute cholecystitis. Grade I can also be defined as acute cholecystitis in a healthy person with no organ dysfunction and mild inflammatory changes in the gallbladder, making cholecystectomy a safe and low-risk operative procedure	

P/A =

RS =

CVS =

CNS =

CBC	LFT	RFT
Hb:	T.Bilirubin:	Urea :
TLC:	D. Bilirubin:	Creatinine :
N/L/E/B/M:	SGOT:	Na:
	SGPT:	K:
NLR:	ALP:	Cl:
PCV:	T. PROTEINS:	HCo3:
Plt:	S. ALBUMIN:	RBS :
NLR:	A:G	hsCRP :
RBC:	PT/INR:	S. Lipase :
Retic C:		S. Amylase :
USG / CT REPORT/MRCP/HPR :		

ANNEXURES- III- PHOTOGRAPH

1. PERCUTANEOUS CHOLECYSTOSTOMY



2. GANGRENOUS GALL BLADDER



[illegible]

SR. NO	IP NUMBER	TOKYO G	CRITERIA	DIAGNOSIS	NAME	AGE	SEX

CAN BE
OMITTED

CAN BE
OMITTED

CONSIDER

CONSIDER

CONSIDER

CAN BE
OMITTED

CONSIDER

CONSIDER

		26
		34
		50

DOA	DOD	HOSP STAY	ICU STAY	BUILT	HISTORY OF PR		
					PAIN		
		DAYS	DAYS		YES/NO	DURATION OF PAIN	NAUSEA

CAN BE
OMITTED

CAN BE
OMITTED

CONSIDER

CONSIDER

CONSIDER

CONSIDER

CONSIDER

CONSIDER

PRESENT ILLNESS			COMORBIDITIES			HABITS	
VOMIT	FEVER	Abd distension	DM	HTN	OTHER	Alcohol	Smoking

CONSIDER CONSIDER CONSIDER CONSIDER CONSIDER CONSIDER CONSIDER CONSIDER

GEN EXAM					SYSTEMICM EX		
TEMP	P	BP	ICTERUS	PALLOR	TENDERNESS	GUARDING	MURPHYS SIGN

CAN BE OMITTED CAN BE OMITTED CAN BE OMITTED CONSIDER CONSIDER CONSIDER CONSIDER CONSIDER

AM		OTHER SYSTEMS				
DISTENSION	BS		HB	TLC	N	L

CONSIDER

CONSIDER

CONSIDER

CONSIDER

CONSIDER

OMIT

OMIT

RESPI SYSTEM MALES 12 TO 16 4000 TO 11000

FEMALES 11 TO 15

INVESTIGATIONS							
ALP	TP	S. ALB	A:G	PT	INR	RBS	HbA1c

CONSIDER CONSIDER CONSIDER OMIT OMIT CONSIDER OMIT CONSIDER

53 - 128 5.70- 8.2 3.2 - 4.8 0.9 TO 2 MAX : 1.4 <6.5
NORMAL

S. AMYLASE	S. LIPASE	HSCRP	UREA	CREAT	NA	K	CL

CONSIDER CONSIDER CONSIDER CONSIDER CONSIDER OMIT OMIT OMIT

<40 <40 TO 5 NORMA 20 TO 40 0.7 TO 1.4 135 TO 150 3.5 5.5

HCO3	HIV	HBSAG	HCV	C/S	SENSITIVITY	BLOOD CS	COVID RAT

OMIT OMIT OMIT OMIT CONSIDER CONSIDER OMIT CONSIDER

USG							
GB							PERICHO
GB	Largest dimension	MULTIPLE / SINGIE	DISTENSION	THCK WALLS	THICKNESS(MM)	HEPATOME GALY	FAT STRANDING

CONSIDER CONSIDER CONSIDER CONSIDER CONSIDER CONSIDER CONSIDER CONSIDER

	CT						
LECYSTIC							
PERICHOLEC YSTIC COLLECTIO N	IHBRD	PERICHOLEC YSTIC COLLECTIO N AND FAT STRANDING	HEPATOME GALY	DILATED CBD	WALL THICKNESS	GB	IHBRD

CONSIDER CONSIDER CONSIDER CONSIDER CONSIDER CONSIDER CONSIDER CONSIDER

MRCP					PCD	SURGERY DONE	HPR
DILATED CBD	WALL THICKNESS	GB	RADIOLOGI CAL DIAGNOSIS	PLEURAL EFFUSION			

CONSIDER CONSIDER CONSIDER CONSIDER CONSIDER CONSIDER CONSIDER CONSIDER

ANTIBIOTICS	OTHER	CT NO
	ERCP DONE	INTRAOP FINDINGS

CONSIDER CONSIDER CONSIDER