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Clinical Outcomes of Delayed Laparoscopic Cholecystectomy in Patients with Acute Calculous Cholecystitis: A Single Centre Study

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Abstract **Original Research Article**

Background: A delayed laparoscopic cholecystectomy is performed as an elective procedure several weeks after a conservative treatment which involves a course of intravenous antibiotics. ***Aims:*** To evaluate the clinical outcomes (i.e. hospital stay, mean operative time, re-admissions, and conversion) of delayed laparoscopic cholecystectomy among patients with acute calculous cholecystitis operated on in a tertiary care hospital. ***Methods:*** A six-month retrospective study was conducted at the Department of Surgery, Saint Luke's General Hospital, Kilkenny, Ireland, from 28th August, 2017, to 1st March, 2018. It included 148 patients with acute calculous cholecystitis who underwent delayed laparoscopic cholecystectomy in the department from January, 2016 to December 2016 and who satisfied the inclusion and exclusion criteria. The data was analyzed using SPSS version 21. The age range of patients was between 26 and 59 years, and the overall mean (±SD) age of patients was 41.67 (± 8.23) years. The majority (59.5%) of patients enrolled were aged over 40 years. Among the 148 patients enrolled in this study, 34 (23%) were males and 114 (77%) were females. Only eight (5.4%) patients were converted to open cholecystectomy, and readmission was observed in 21.6% patients. The mean (SD) length of stay was 5.59 (4.42), while the mean length of operative duration was 107.69 (32.15) respectively. ***Conclusion***: Delayed laparoscopic cholecystectomy among patients with acute calculous cholecystitis produces a significantly lower likelihood of conversion to open surgery.

Keywords: Delayed laparoscopic cholecystectomy, open cholecystectomy, acute calculous cholecystitis, readmission, length of stay.

INTRODUCTION

Acute calculous cholecystitis is caused by initial sterile inflammation as a result of cystic duct obstruction which is followed by secondary bacterial infiltration [1]. Clinical symptoms include right upper quadrant abdominal pain, fever, nausea, and vomiting [2]. Right upper quadrant tenderness is noted on physical examination [2]. Laboratory findings include elevated white cell count and C-reactive protein [3]. Ultrasonography can support the diagnosis by demonstrating a distended gallbladder filled with gallstones, increased thickness of the gallbladder wall, or pericystic fluid [3]. Acute calculous cholecystitis is one of the most common diseases encountered in general surgery [4]. Gallstones are present in up to 15% of the adult population and 4% of these patients become symptomatic every year [5]. More than half a million cholecystectomies are performed in the USA each year, and almost all are due to symptomatic cholelithiasis [6].

A delayed laparoscopic cholecystectomy (LC) is performed as an elective procedure several weeks after conservative treatment with a course of intravenous antibiotics [5]. There is more and more evidence suggesting that delayed LC has some disadvantages, namely longer length of hospital stay, increased hospital costs, and several associated complications, including longer and more frequent readmissions, as well as increased 30-day morbidity and mortality rates [7-9].

A retrospective study that evaluated the advantages and limitations of delayed laparoscopic cholecystectomies (DLC) performed in a tertiary centre for ten years reported that the rate of conversion to open surgery was 5.8%, mean length of stay was 20.6 days, and 30 days mortality was 0.6% [10]. A recent meta-analysis which assessed 244 patients who had undergone delayed laparoscopic cholecystectomy reported that the length of stay was 9 days, conversion to open surgery was 22.1%, and bile duct injury occurred at a rate of 0.6% [5]. Moreover, another meta-analysis which

evaluated a larger number of patients (816) treated with delayed laparoscopic cholecystectomy reported the overall length of stay as 8.3 days, conversion to open surgery as 13.1%, and mortality as 0.3% [11]. Gutt *et al.*, reported in their 2013 study that the overall length of stay was 10 days and conversion to open surgery was 10.5% [12]. Thus, the studies conducted to date have shown variations in the length of stay, conversion to open surgery, and mortality among patients who underwent delayed laparoscopic cholecystectomies (LC). It is also notable that certain important indicators of clinical outcomes (i.e. readmissions and operative duration) have not been identified.

Performing early laparoscopic cholecystectomies would require changes in both hospitals' logistics and their infrastructure. Evidence from the literature did not reveal any differences in bile duct injury and mortality between early and delayed laparoscopic cholecystectomy that would justify these changes. However, because clinical outcomes (i.e. conversion to open surgery, operative time, length of stay, and readmissions) related to delayed laparoscopic cholecystectomy have not been well investigated in existing research, indicators of clinical outcomes (i.e. readmissions and operative duration) have not being identified. To rectify this gap in understanding, this study was planned, using retrospective data which covered a one-year period after patients had been admitted and operated on for acute calculous cholecystitis through delayed laparoscopic cholecystectomy. This data was included to allow better evaluation of the treatment strategy's effectiveness in terms of clinical outcomes.

LITERATURE REVIEW

Carl Johann August Langenbuch (1846–1910) performed the first open cholecystectomy in Berlin in 1882 on a 43-year-old man [13]. In 1911, Hans Christian Jacobaeus reported his 10-year experience of inspecting both abdominal and chest cavities, without pneumoperitoneum, and he called the technique 'laparothorakoskopoe', a name derived from the Greek words 'lapara' (meaning the part of the body corresponding to the abdomen), 'thoraco' (chest) and 'skopein' (meaning to look at) [13]. During the 1960s and 1970s, laparoscopy use in the area of gynaecology became immensely popular, and Kurt Semm, one of the pioneers of laparoscopic surgery, performed the first laparoscopic appendicectomy using a suture technique in 1980 [13].

Despite laparoscopy's promise as the future of general surgery, it did not gain immediate popularity because of the prevailing dogma which suggested that 'the larger the cut, the better the surgeon' [13]. However, Maurett's performance of the first laparoscopic cholecystectomy in 1987 changed the entire future of the practice of surgery. The shift has been so phenomenal that laparoscopic surgical skills are currently part of all standard surgical training courses [13].

The widespread acceptance of laparoscopic cholecystectomy can be attributed to the fact that postoperative pain is reduced, recovery is more rapid, cosmetic results are better, hospital stays are shorter, and the return to work for patients is quicker than with the open procedure. However, laparoscopic cholecystectomy is not without complications, which can include iatrogenic injury to the biliary tree, biliary leakage, bowel perforation, retained stones, postoperative shoulder tip pain, fever, and ileus [13-16].

These complications are more likely to occur in the context of acute calculous cholecystitis, though the pathophysiology of this is poorly understood and no single factor can be pinpointed as being responsible for this issue. To fully comprehend the aetiology of changes happening in acute cholecystitis, we need to fully understand the anatomical and pathophysiological characteristics of the hepatobiliary system and diaphragm [17-19].

The Anatomy of the Liver and Gallbladder

The biliary tract is the conduit between the liver and the duodenum and is designed to store and transport bile, under the control of neuronal and hormonal regulation. Bile is formed in the hepatocytes and steadily secreted into canaliculi, which transport it to the larger extrahepatic ducts. The sphincter of Oddi regulates the flow of bile into the duodenum or to the cystic duct and the gallbladder. When stimulated, the gallbladder contracts steadily, the sphincter relaxes, and bile flow into the duodenum increases.

In order to explain the anatomy and physiology of the biliary tract and the production of bile, it is necessary to briefly outline the anatomy of the liver. The liver is divided macroscopically into right and left lobes by the falciform ligament anteriorly. Inferiorly, this corresponds to the round ligament and umbilical fissure. The right lobe is further divided by the gallbladder fossa into the right hemiliver, to the right of the gallbladder, and the quadrate lobe to the left. The fourth lobe (caudate) is posterior and surrounds the inferior vena cava. Hence, anatomically, the liver is divided into two main lobes and two accessory lobes [20].

The concept of functional anatomy has developed as understanding of liver function has improved. Improvements in understanding were initiated by Cantlie in 1898 and subsequently enhanced by McIndoe in 1929, Ton That Tung in 1939, and Couinaud in 1957 (Figure 1) [21]. In December 1998, the Scientific Committee of the International Hepato-Pancreato Biliary Association created a terminology committee to deal with confusion about the nomenclature of hepatic anatomy and liver resections. The new terminology formulated by this committee and now internationally accepted is known as 'The Brisbane 2000 Terminology of Liver Anatomy and Resections' [20]. It is

anatomically and surgically correct, consistent, self-explanatory, linguistically correct, precise, and concise.

The Brisbane terminology identifies three functional livers: the right, the left. and the caudate. The separation between the right and left hemilivers is at Cantlie's line, which is an oblique plane extending from the centre of the gallbladder bed to the left border of the inferior vena cava. The middle hepatic vein runs in this plane, which is an important radiological landmark [22].

The right hemiliver is divided further into two sections by the right portal scissura (anterior and posterior sections), within which runs the right hepatic vein. Each section is then divided on the basis of its blood supply and bile drainage mechanisms into two segments. The anterior section is divided into segment 5 (inferior) and segment 8 (superior) while the posterior section is divided into segment 6 (inferior) and segment 7 (superior).

Meanwhile, the left hemiliver is divided into three segments. Segment 4 (the quadrate lobe), which is known as the left medial section, lies to the right of the falciform ligament. Its right margin forms the right margin of the left hemiliver. Segment 3, which lies in the anterior part, and segment 2, which lies in the posterior part of the left hemiliver, form the left lateral section. The left lateral section lies on the left of the falciform ligament. The left hepatic vein runs between segments 2 and 3 [22].

The caudate hemiliver (segment 1) is considered separately because of its separate blood supply and venous and bile drainage mechanisms.

Blood Supply and Venous Drainage

The arterial supply to the liver in early gestational life is from three main sources, which are the left hepatic artery from the left gastric artery; the middle hepatic artery (common hepatic artery) from the coeliac trunk; and the right hepatic artery from the superior mesenteric artery. After further development, the blood supply assumes the adult pattern, with atrophy of both the right and left hepatic arteries, and the common hepatic artery (middle hepatic) then supplies the whole liver. This adult pattern occurs in around 67% of individuals. The common hepatic artery branches into the right and left hepatic arteries, which supply the right and left hemilivers, respectively. In 90% of cases, segment 4 is supplied by a named branch (middle hepatic) from either the right or left hepatic artery (45% each). The other variations that occur are as follows [23]:

- The common hepatic supplying the right liver and the left hepatic arising from the left gastric (8%).
- The common hepatic supplying the left liver and the right hepatic arising from the superior mesenteric artery (11%).
- Persistence of all three arteries (3%).
- Atrophy of the common hepatic artery (12%), with the liver supplied by the:
    - right hepatic in 9%
    - left hepatic in 1%
    - both right and left in 2%.

The left hepatic artery arising from the left gastric artery is usually easy to identify in the gastrohepatic ligament. The right hepatic artery arising from the superior mesenteric artery, on the other hand, is more variable. It ascends behind the pancreas in relation to the portal vein, and it assumes a posterior location in the portal pedicle, usually slightly to the left of the portal vein [23].

The venous drainage of the liver is into the inferior vena cava through the right, middle, and left hepatic veins. The union of superior, middle, and inferior branches usually forms the right vein, where the superior is the largest branch [24].

The right hepatic vein trunk joins at the right margin of the vena cava at a point separate from and slightly above the trunk that is formed by the middle and left vein. The middle hepatic vein forms from two veins arising from segment 4 and segment 5 [25].

The middle hepatic vein joins the left hepatic vein to form a common trunk before draining into the vena cava in 90% of people. The left hepatic vein is more variable and is usually formed by the union of the branches from segments 2, 3, and 4 [25].

Intrahepatic Bile Ducts

There are more than 2km of bile ductules and ducts in the adult human liver. These structures are far from being inert channels, and they are capable of significantly modifying biliary flow and composition in response to hormonal secretion. Bile secretion starts at the level of the bile canaliculus, the smallest branch of the biliary tree. These structures form a meshwork between hepatocytes with many anastomotic interconnections. Bile then enters the small terminal bile ductules (canals of Hering), which provide a conduit through which bile may traverse to enter the larger perilobular or interlobular bile ducts. The interlobular bile ducts form a richly anastomosing network that closely surrounds the branches of the portal vein. These ducts increase in calibre and the smoothness of the muscle fibres within their walls as they reach the hilus of the liver [23].

Furthermore, as these ducts become larger, the epithelium becomes increasingly thick and contains many elastic fibres. These ducts anastomose to form the segmental branches (from segment 1 to segment 8). In 80 to 85% of individuals, these segmental branches anastomose to form the anterior (segments 5 and 8) and posterior sectorial bile ducts (segments 6 and 7) in the right hemiliver [24].

With the union of these two sectorial ducts, in 57% of individuals, the right hepatic duct is formed and is usually short (approximately 9mm in length). In the left hemiliver, the second and third segmental branches anastomose to form the left hepatic duct in the region of the umbilical fissure. The anastomosis of segment 4 to the left hepatic duct usually occurs as a single trunk to the right of the umbilical fissure, and this is the case for 67% of individuals. The left hepatic duct is generally longer and more surgically accessible than the right hepatic duct [24].

The caudate lobe (segment 1) is drained by both right and left hepatic ducts. It also draws its arterial supply from both the right and left portal veins and the hepatic artery, with small venous branches draining directly to the inferior vena cava [24].

The anatomy of this third hemiliver is revealed in certain pathologic conditions, such as Budd–Chiari syndrome, where the outflow of the three hepatic veins is obstructed, leading to diversion of blood to the caudate lobe which results in hypertrophy [24].

Extrahepatic Bile Ducts

The joining of the right and left hepatic ducts forms the common hepatic duct. The accessory biliary apparatus, which is composed of the gallbladder and cystic duct, joins the common hepatic duct to form the common bile duct and this drains bile into the duodenum. This comprises the extra-hepatic biliary system [25].

The biliary confluence takes place at the right of the hilus of the liver, anterior to the portal venous bifurcation and overlying the origin of the right branch of the portal vein. The biliary confluence is separated from the posterior aspect of segment 4 of the left liver by the hilar plate, which is the fusion of connective tissue enclosing the biliary and vascular structures with Glisson's capsule [24].

The Gallbladder and the Cystic Duct

The gallbladder is a reservoir of bile in the shape of a piriform sac which is partly contained in a fossa on the inferior surface of the right hepatic lobe. It extends from the right extremity of the porta-hepatis to the inferior border of the liver. It is 7 to 10cm long and 3 to 4cm wide at its broadest point, and it can hold from 30 to 50ml. The gallbladder is divided into a fundus, body, infundibulum, and neck. The fundus extends about 1cm beyond the free edge of the liver, and the body is the gallbladder's largest segment, while the infundibulum is the transitional area between the body and the neck [24].

Hartmann's pouch is a bulge on the inferior surface of the infundibulum. Gallstones may become impacted here and can cause obstruction of the cystic duct. The neck is the narrow tapered segment of the infundibulum which joins the cystic duct.

The cystic duct is 3 to 4cm long and passes, posteriorly inferior and to the left, from the neck of the gallbladder to join the common hepatic duct to form the common bile duct (CBD). The mucosa of the cystic duct is arranged with spiral folds known as the valves of Heister.

A number of anomalies occur in the gallbladder and can be described as congenital (e.g. phyrygian cap, duplication, bilobed gallbladder), diverticulum, hypoplasia or absent gall bladder, abnormal position (falciform ligament, intrahepatic, left sided) and abnormal mesentry. Furthermore, the cystic duct inserts into the bile duct at a variety of sites.

The *arterial supply* to the gallbladder is from the cystic artery. Because the cystic artery is an end artery, the gallbladder is more susceptible to ischemic injury and necrosis as a result of inflammation or interruption of the artery. The cystic artery can originate from the right hepatic, left hepatic, or the common hepatic artery, and it can be anterior or posterior to the common hepatic duct [25].

The *venous drainage* is through the cystic vein, which drains into the portal vein. There are also some small veins that drain directly into the liver to the hepatic veins [25].

The *lymphatic drainage* of the gallbladder proceeds mainly by four routes, which form two pathways that drain in the thoracic duct [24]:

1. Superior and external, drains the fundus (around 6% of cases).
2. Superior and medial, drains the medial aspect of the gallbladder (around 10% of cases).
3. Inferior and external, drains the body of the gallbladder (present in 82% of cases).
4. Inferior and medial, from the body of the gallbladder (constant).

While the other three routes drain to both pathways, the inferior and external route drains only to the inferior pathway. This is important in cases of gallbladder cancer, which can spread to the liver, because its extensive lymph drainage to both pathways can make cure by radical surgery difficult [20].

The duct of Luschka – a small bile duct which runs in the bed of the gallbladder, outside the wall – is present in 50% of individuals. This duct is surgically significant because it may be injured during cholecystectomy and may result in bile fistula unless ligated. Recent reports have demonstrated a 1.5 to 2.0% incidence of bile leakage from the duct of Luschka after laparoscopic cholecystectomy. Ligation has no consequences as the duct of Luschka is an end duct that drains an isolated segment.

The Common Bile Duct

The cystic duct and the common hepatic duct join to form the common bile duct. Its course is divided into supraduodenal, retroduodenal, pancreatic and intraduodenal segments, and the duct joins the main pancreatic duct to form the sphincter of Oddi [24].

The supraduodenal segment usually lies in the free border of the hepatoduodenal ligament. It runs to the right of the hepatic artery and anterior to the portal vein. The retroduodenal segment descends posterior to the first part of the duodenum and runs slightly obliquely from right to left. The pancreatic segment is related to the head of the pancreas, and it can either run entirely retropancreatically or travel through its parenchyma.

The diameter of the common bile duct is often used as an indication of biliary pathology. Its 'normal' size varies, depending on the modality used to measure it, and a range of 4 to 13mm has been reported. The most common modality used to examine the common bile duct diameter is ultrasound, and a diameter up to 6mm is considered normal. Some consider the equivalent in contrast radiology to be 10mm, though this depends on the magnification [24].

Blood Supply

The blood supply to the common bile duct is also divided into three segments [24]. The supraduodenal segment of the duct essentially has an axial blood supply, which originates from the retroduodenal, right hepatic artery, cystic, gastroduodenal, and the retroportal arteries. On average there are eight small arteries, with the main two running along the side of the common bile duct at 3 and 9 o'clock. Sixty percent of the arterial blood supply occurs from the duodenal end of the duct, and 38% is from the hepatic end. Only 2 percent of the arterial supply is non-axial, arising directly from the main hepatic trunk. The second segment, which is the retropancreatic part of the duct, is supplied by the retroduodenal artery. It provides blood to the multiple small vessels which run around the duct to form a mural plexus. The third segment is the hilar duct, and it receives its blood supply from the surrounding blood vessels, forming a rich network.

The veins draining the bile duct correspond to the described arteries. They drain into veins at 3 and 9 o'clock on the side of the common bile duct.

Lymphatic Drainage

The lymphatic drainage of the extrahepatic biliary system occurs through two pathways [24]:

1. The superior pathway of nodes along the cystic duct, the hepatic duct, the anterior and medial aspects of the portal vein, and the coeliac axis.
2. The inferior pathway of nodes along the cystic duct, anterior and lateral aspects of the portal vein, the posterior aspect of the pancreas, between the aorta and the inferior vena cava, and the left aspect of the aorta under the left renal vein.
3. Lymph drainage of the common bile duct uses lymph nodes along the duct to both the inferior and superior pathways.

Calot's Triangle

Calot's triangle is an anatomical region bounded medially by the common hepatic duct, inferiorly by the cystic duct, and superiorly by the inferior surface of the liver [20]. The cystic artery runs within this triangle. Two anomalies may be encountered in Calot's triangle. Firstly, an aberrant right hepatic artery, which arises from the superior mesenteric artery, is seen in 16% of individuals. It can be located in the medial border of Calot's triangle in 90% of these patients. Secondly, the right posterior or anterior sectoral ducts may run through Calot's triangle and may be mistaken for the cystic duct.

It has been well demonstrated that, during cholecystectomy, the cystic artery can safely and easily be identified at the junction of the gallbladder neck and the cystic duct by defining the cystic lymph node. The node may be swept in the direction of the common bile duct to facilitate recognition of the cystic duct and the cystic artery.

The Anatomy of the Diaphragm

The diaphragm is a dome-shaped, thin, muscular, and tendinous septum that separates the chest cavity above from the abdominal cavity below [24]. It is pierced by structures that pass between the chest and abdomen.

Origin

Sternal part — arising from the posterior surface of the xiphoid process by two fleshy slips.
Costal part — arising from the deep surfaces of the lower six ribs and their costal cartilages.
Vertebral (Lumbar) part — arising from the medial and lateral lumbocostal arches (arcuate ligament) and from the lumbar vertebrae by the right and left crura.

The right crus arises from the sides of the bodies of the three lumbar vertebrae and intervertebral discs, while the left crus arises from the sides of the body of the first two lumbar vertebrae and intervertebral discs.

Lateral to the crura, the diaphragm arises from the medial and lateral arcuate ligaments. The medial arcuate ligament extends from the side of the body of the second lumbar vertebra to the tip of the transverse process of the first lumbar vertebra. The lateral arcuate ligament extends from the tip of the transverse process of the first lumbar vertebra to the lower border of the 12th rib.

The medial borders of the two crura are connected by a median arcuate ligament, which crosses over the anterior surface of the aorta.

Insertion

The diaphragm is inserted into a central tendon, which is shaped like three leaves. The superior surface of the tendon is partially fused with the inferior surface of the fibrous pericardium. Some of the muscle fibres in the right crus pass up to the left and surround the esophageal orifice in a sling-like loop. These fibres appear to act as a sphincter, and they possibly assist in preventing the regurgitation of stomach contents into the thoracic part of the esophagus (Figure 2).

The Diaphragm's Nerve Supply

Motor nerve supply – the right and left phrenic nerves (C3, 4, 5)

Sensory nerve supply – the parietal pleura and peritoneum covering the central surfaces of the diaphragm are from the

Phrenic nerves and the periphery of the diaphragm is from the lower six intercostals nerves.

In addition to the diaphragm, the phrenic nerve also supplies sensory fibres to mediastinal and diaphragmatic pleurae, the fibrous pericardium, the parietal layer of the serous pericardium, and the part of the parietal peritoneum that lies below the central part of the diaphragm through its communication with phrenic branches of the coeliac plexus. The phrenic is also distributed to the falciform and coronary ligaments of the liver, the inferior vena cava, the supra-renal glands and possibly the gall bladder.

Applied Anatomy

Shoulder-tip pain — Irritation of the diaphragm may cause referred pain in the shoulder because phrenic and supraclavicular nerves have the same root values.

Hiccoughs — These results of spasmodic contraction of the diaphragm may be (a) peripheral, due to local irritation of the diaphragm or its nerves, or (b) central, due to irritation of the hiccough centres in the medulla.

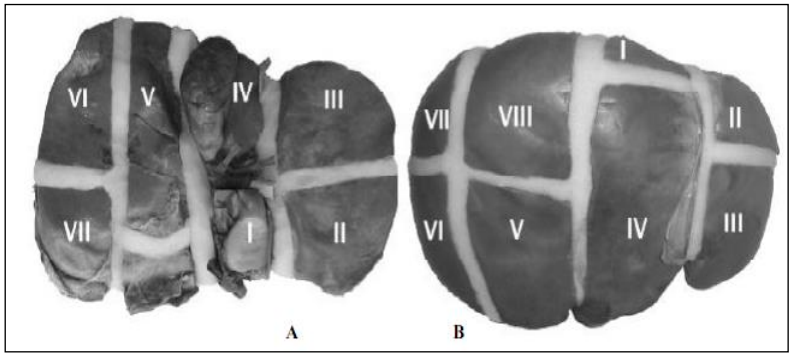


Figure 1: Couinaud's Classification [24]

(A – visceral surface; B – diaphragmatic surface. Segment I – caudate lobe; segment II corresponds to the left lateral sector; segments III and IV – to the left paramedian sector; segments V and VIII – to the right paramedian; segments VI and VII – to the right lateral sector)

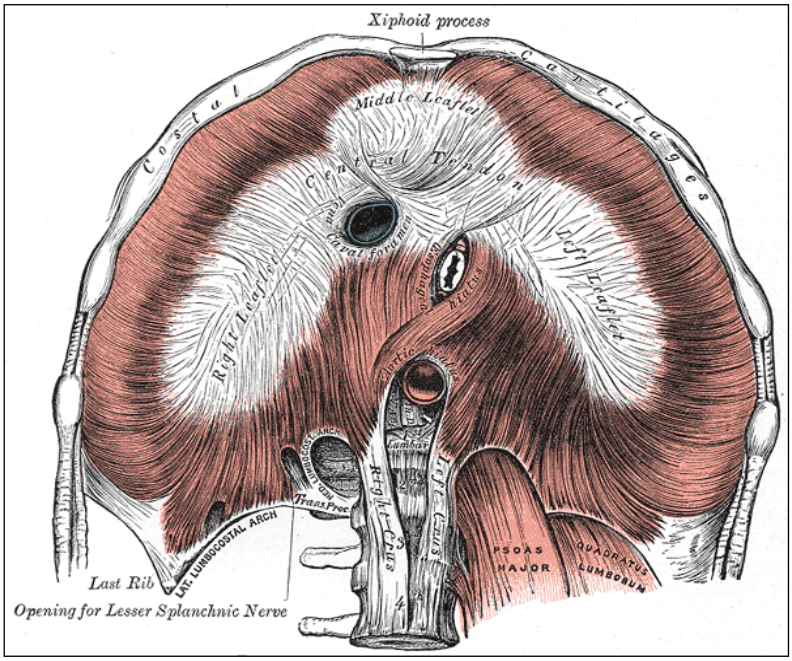


Figure 2: The Anatomy of the Diaphragm [26]

Objective

To evaluate the clinical outcomes (i.e., hospital stay, mean operative time, readmissions, and conversion) of delayed laparoscopic cholecystectomy among patients with acute calculous cholecystitis operated in a tertiary care hospital.

Operational Definitions

Acute Calculous Cholecystitis

Defined as absence of gall stones along with features of acute cholecystitis, acute cholecystitis was diagnosed on the basis of following ultrasonographic findings [46]:

- Thickened gall bladder wall (>4mm)
- Enlarged gall bladder (long axis diameter >8cm, short axis diameter >4cm)
- Pericholecystic fluid collection

Presence of any two of the above three criteria was considered to indicate acute cholecystitis in this study.

Delayed laparoscopic cholecystectomy

Delayed laparoscopic cholecystectomy was defined as routine laparoscopic cholecystectomy, which was performed six weeks after the index admission following a conservative treatment with a course of intravenous antibiotics [5].

Conversion to open cholecystectomy

Surgeries where laparoscopic cholecystectomy was initially planned but converted to open due to safety concerns for patients. In such procedures, the abdomen was opened to permit cholecystectomy – removal of the gallbladder [5].

Operative Duration

Operative duration (minutes) was measured from the time of insertion of the Veress needle to closure of the trocar insertion site [47].

Length of stay

Length of hospital stay was measured in days, from the day of surgery to the day of discharge [5].

Readmission

Any admission after 24 hours of discharge following the delayed laparoscopic cholecystectomy procedure was considered as readmission [5].

Previous Abdominal Surgery

Patients who had a lower midline scar due to previous surgery which had been conducted more than 1 year previously [5].

Diabetes and Hypertension

Patients with known *diabetes* (fasting blood glucose concentration exceeding 126mg/dl on two different occasions) and *hypertension* (systolic pressure greater than 140mm Hg or a diastolic pressure greater than 90mm.

METHODS

Study Setting

Department of Surgery, Saint Luke's General Hospital, Kilkenny, Ireland.

Duration of Study

Six months from 28th August, 2017 to 1st March, 2018.

Sample Size

Given that the study was retrospective, a sample size was not calculated. The study covered the total number of patients (148) with acute calculous cholecystitis who underwent delayed laparoscopic cholecystectomy during the one-year period from January, 2016, to December, 2016, at the Department of Surgery, Saint Luke's General Hospital; Kilkenny, Ireland.

Sampling Technique

All patients (148 patients) with acute calculous cholecystitis who underwent delayed laparoscopic cholecystectomy and satisfied the inclusion and exclusion criteria during the study period were included in this retrospective study.

Inclusion Criteria

The following patients were included in the study:

- Patients with an acute calculous cholecystitis diagnosis on ultrasonography.
- Patients who underwent delayed laparoscopic cholecystectomy (identified on case record).
- Patients older than 18 years of age and less than or equal to 60 years of age.

Exclusion Criteria

The following patients were excluded from the study:

- Patients presenting with choledocholithiasis identified on case records were excluded.
- Patients diagnosed with acute cholangitis were excluded.
- Patients with co-morbid conditions identified on case records, such as coagulopathies, Chronic Obstructive Pulmonary Disease (COPD), acute myocardial infarction (AMI) and cirrhosis were also excluded.

Study Design

Retrospective study.

Data Collection Procedure

This study was initiated after approval from the College of Physicians and Surgeons Pakistan. The retrospective study included 148 patients with acute calculous cholecystitis who underwent delayed laparoscopic cholecystectomy from January, 2016, to December, 2016, at the Department of Surgery, Saint Luke's General Hospital, Kilkenny, Ireland and who satisfied the inclusion and exclusion criteria.

Only cases of delayed laparoscopic cholecystectomy conducted with the widely accepted four-port technique were included. All patients received one dose of intravenous (IV) Levofloxacin (500 mg) at the time anaesthesia was induced, with surgery being performed under general anaesthesia. Surgeries performed by a surgeon who had experience in similar settings for five years were included.

All findings were recorded in the pre-designed pro forma. Each study participant's age, gender, and status in terms of Body Mass Index, hypertension, diabetes, and previous abdominal surgery were recorded in a yes/no format. Moreover, operative duration, conversion to open cholecystectomy, length of post-operative and readmissions after 24 hours following discharge from the delayed laparoscopic cholecystectomy procedure were also recorded.

Ethical Considerations

The study was conducted according to the ethical guidelines set out in the Helsinki Declaration. The anonymity and confidentiality of participants' data was maintained throughout the research. No unauthorised person had any access to the patients' data.

Data Analysis

Data was entered and analysed by using SPSS version 21. Mean and standard deviations were computed for numerical variables, such as age, length of stay, and operative duration, whereas, frequency and percentages were used to present categorical variables including gender, Body Mass Index, and patients' histories of hypertension, diabetes, previous surgery, conversion to open cholecystectomies, and readmissions.

Stratification of binary outcome variables (i.e., conversion to open cholecystectomy and readmission) and continuous outcome variables (operative duration and length of post-operative stay) were performed with regard to age categories, gender, BMI categories, previous abdominal surgery and co-morbidities (i.e., diabetes and hypertension). In order to control the effects of these confounders on the outcome variables, chi-square tests for binary outcomes and independent t-tests for continuous outcomes were used. A P-value ≤ 0.05 was taken to represent significance.

RESULTS

One hundred and forty eight patients with acute calculous cholecystitis who underwent delayed laparoscopic cholecystectomy from January, 2016 to December, 2016 at Department of Surgery, Saint Luke's General Hospital, Kilkenny, Ireland, and who satisfied the inclusion and exclusion criteria, were included in this retrospective study. Between 30th March, 2015, and 3rd November, 2015, 310 patients indicated for cholecystectomy who satisfied the inclusion criteria were recruited into the study. The clinical outcomes (i.e. hospital stay, mean operative time, readmissions and conversion) of patients with acute calculous cholecystitis who underwent delayed laparoscopic cholecystectomy were noted.

The age range of patients was between 26 and 59 years, and the overall mean (±SD) age of patients was 41.67 (± 8.23) years. A majority (59.5%) of the enrolled patients were aged over 40 years, while 40.5 percent of enrolled patients were aged less than or equal to 40 years (Table 1).

Among the 148 patients enrolled in this study, 34 (23%) were males and 114 (77%) were females (Graph 1). The overall male to female ratio was 1:3.4 (Graph 1).

Among the 148 patients enrolled, fifty (33.8%) had a BMI either less than or equal to 25, and the majority (98, 66.2%) had a BMI greater than 25 (Graph 2). Meanwhile, 50 (33.8%) patients were hypertensive while only thirteen (8.8%) were diabetic (Tables 2-3). The majority of patients (112, 75.7%) had no history of previous abdominal surgery (Table 4).

Importantly, only eight patients (5.4%) were converted to open cholecystectomy. Readmissions accounted for thirty two (21.6%) patients. The mean (SD) length of stay was 5.59 (4.42) and 62 (41.9%) patients had a length of stay greater than 4 days. The mean (SD) operative duration was 107.69 (32.15), with around 106 (71.6%) patients having an operative duration of more than 90 minutes. (Tables 5-8).

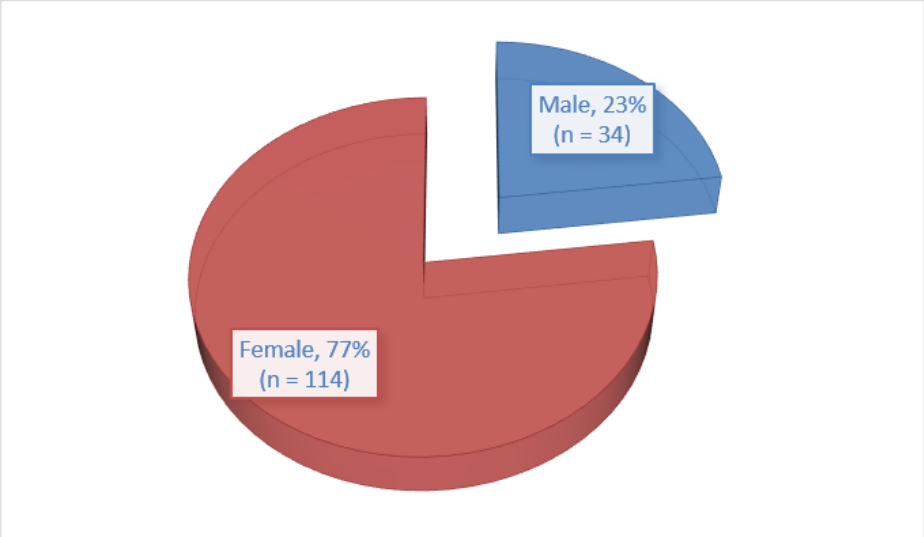
At the data analysis stage, conversion to open cholecystectomy was stratified with respect to age categories, gender, BMI categories, and history of hypertension, diabetes, and previous abdominal surgery (Tables 9-14). The readmission of patients was also stratified in this way (Tables 15-20).

The operative duration was compared across age categories, gender, BMI categories, hypertension, diabetes, and previous abdominal surgery (Tables 21-26). Finally, the length of stay was compared across age categories, gender, BMI categories, and experience of hypertension, diabetes, and previous abdominal surgery (Tables 27-32).

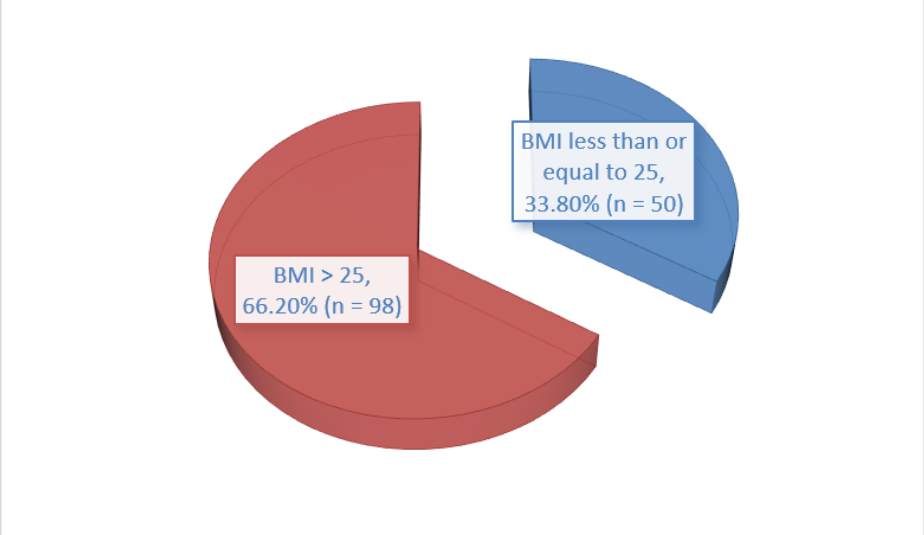
Table 01: Age Distribution (n = 148)

Age in years	N	Percentage (%)
≤ 40	60	40.5
> 40	88	59.5

Overall mean age (±SD) = 41.67 (± 8.23)



Graph 01: Gender Distribution (n= 148)



Graph 02: Body Mass Index Distribution (n= 148)

Table 02: Hypertension Distribution (n = 148)

Hypertension	n	Percentage (%)
Yes	50	33.8
No	98	66.2

Table 03: Diabetes Distribution (n = 148)

Diabetes	n	Percentage (%)
Yes	13	8.8
No	135	9.2

Table 04: Previous Abdominal Surgery Distribution (n = 148)

Previous Abdominal Surgery	n	Percentage (%)
Yes	36	24.3
No	112	75.7

Table 05: Conversion to Open Cholecystectomy (n = 148)

Conversion to Open Cholecystectomy	n	Percentage (%)
Yes	8	5.4
No	148	94.6

Table 06: Readmission Distribution (n = 148)

Readmission	N	Percentage (%)
Yes	32	21.6
No	116	78.4

Table 07: Length of Stay Distribution (n = 148)

Length of Stay (days)	n	Percentage (%)
≤ 4 Days	86	58.1
> 4 Days	62	41.9

Overall mean age (±SD) = 5.59 (± 4.42)

Table 08: Operative Duration Distribution (n = 148)

Operative duration (minutes)	N	Percentage (%)
≤ 90 minutes	42	28.4
> 90 minutes	106	71.6

Overall mean age (±SD) = 107.69 (± 32.15)

Table 09: Conversion Rate with Respect to Age Categories (n=148)

Age (years)	Conversion to Open		P-value
	Yes n (%)	No n (%)	
≤ 40	6 (75)	54 (38.6)	0.062
> 40	2 (25)	86 (61.4)	

Data is shown in numbers followed by percentages in parentheses

Table 10: Conversion Rate with Respect to Gender (n=148)

Gender	Conversion to Open		P-value
	Yes n (%)	No n (%)	
Male	2 (25)	32 (22.9)	0.889
Female	6 (75)	108 (77.1)	

Data is shown in numbers followed by percentages in parentheses

Table 11: Conversion Rate with Respect to Bmi Categories (n=148)

BMI categories (Kg/m^2)	Conversion to Open		P-value
	Yes n (%)	No n (%)	
≤ 25	5 (62.5)	45 (32.1)	0.120
> 25	3 (37.5)	95 (67.9)	

Data is shown in numbers followed by percentages in parentheses

Table 12: Conversion Rate with Respect to Hypertension Categories (n=148)

Hypertension	Conversion to Open		P-value
	Yes n (%)	No n (%)	
Yes	6 (75)	44 (31.4)	0.018
No	2 (25)	96 (68.6)	

Data is shown in numbers followed by percentages in parentheses

Table 13: Conversion Rate with Respect to Diabetes Categories (n=148)

Diabetes	Conversion to Open		P-value
	Yes n (%)	No n (%)	
Yes	1 (12.5)	12 (8.6)	0.703
No	7 (87.5)	128 (91.4)	

Data is shown in numbers followed by percentages in parentheses

Table 14: Conversion Rate with Respect to Previous Abdominal Surgery (n=148)

Previous abdominal surgery	Conversion to Open		P-value
	Yes n (%)	No n (%)	
Yes	6 (75)	30 (21.4)	0.003
No	2 (25)	110 (78.6)	

Data is shown in numbers followed by percentages in parentheses

Table 15: Readmission with Respect to Age Categories (n=148)

Age (years)	READMISSION		P-value
	Yes n (%)	No n (%)	
≤ 40	17 (53.1)	43 (37.1)	0.101
> 40	15 (46.9)	73 (62.9)	

Data is shown in numbers followed by percentages in parentheses

Table 16: Readmission with Respect to Gender (n=148)

Gender	READMISSION		P-value
	Yes n (%)	No n (%)	
Male	9 (28.1)	25 (21.6)	0.434
Female	23 (71.9)	91 (78.4)	

Data is shown in numbers followed by percentages in parentheses

Table 17: Readmission with Respect to Bmi Categories (n=148)

BMI categories (Kg/m^2)	READMISSION		P-value
	Yes n (%)	No n (%)	
≤ 25	12 (37.5)	38 (32.8)	0.675
> 25	20 (62.5)	78 (67.2)	

Data is shown in numbers followed by percentages in parentheses

Table 18: Readmission with Respect to Hypertension Categories (n=148)

Hypertension	READMISSION		P-value
	Yes n (%)	No n (%)	
Yes	13 (40.6)	37 (31.9)	0.401
No	19 (59.4)	79 (68.1)	

Data is shown in numbers followed by percentages in parentheses

Table 19: Readmission with Respect to Diabetes Categories (n=148)

Diabetes	READMISSION		P-value
	Yes n (%)	No n (%)	
Yes	3 (9.4)	10 (8.6)	0.894
No	29 (90.6)	106 (91.4)	

Data is shown in numbers followed by percentages in parentheses

Table 20: Readmission with Respect to Previous Abdominal Surgery (n=148)

Previous Abdominal Surgery	READMISSION		P-value
	Yes n (%)	No n (%)	
Yes	10 (31.2)	26 (22.4)	0.353
No	22 (68.8)	90 (77.6)	

Data is shown in numbers followed by percentages in parentheses

Table 21: Operative Duration with Respect to Age Categories (n=148)

Age categories (years)	OPERATIVE DURATION	P-value
≤ 40 years	105.03 ± 30.61	0.409
> 40 years	109.50 ± 33.22	

Data is shown in Mean ± Standard deviation

Table 22: Operative Duration with Respect to Gender (n=148)

GENDER	OPERATIVE DURATION	P-value
Male	111.76 ± 37.09	0.402
Female	106.47 ± 30.61	

Data is shown in Mean ± Standard deviation

Table 23: Operative Duration with Respect to Bmi Categories (n=148)

BMI categories	OPERATIVE DURATION	P-value
< 25	104.84 ± 32.94	0.443
> 25	109.14 ± 31.82	

Data is shown in Mean ± Standard deviation

Table 24: Operative Duration with Respect to Hypertension (n=148)

HYPERTENSION	OPERATIVE DURATION	P-value
Yes	111.72 ± 33.292	0.277
No	105.63 ± 31.53	

Data is shown in Mean ± Standard deviation

Table 25: Operative Duration with Respect to Diabetes (n=148)

Diabetes	OPERATIVE DURATION	P-value
Yes	110.92 ± 44.79	0.706
No	107.38 ± 30.88	

Data is shown in Mean ± Standard deviation

Table 26: Operative Duration with Respect to Previous Abdominal Surgery (n=148)

Previous abdominal surgery	OPERATIVE DURATION	P-value
Yes	108.39 ± 28.77	0.881
No	107.46 ± 33.29	

Data is shown in Mean ± Standard deviation

Table 27: Length Of Stay with Respect to Age Categories (n=148)

Age categories (years)	Length of Stay	P-value
≤ 40 years	6.22 ± 4.75	0.158
> 40 years	5.17 ± 4.16	

Data is shown in Mean ± Standard deviation

Table 28: Length of Stay with Respect to Gender (n=148)

Gender	Length of Stay	P-value
Male	7.29 ± 5.73	0.010
Female	5.09 ± 3.83	

Data is shown in Mean ± Standard deviation

Table 29: Length of Stay with Respect to Bmi Categories (n=148)

BMI categories	Length of Stay	P-value
< 25	6.12 ± 4.45	0.303
> 25	5.33 ± 4.40	

Data is shown in Mean ± Standard deviation

Table 30: Length of Stay with Respect to Hypertension (n=148)

Hypertension	Length of Stay	P-value
Yes	7.34 ± 5.64	0.001
No	4.70 ± 3.34	

Data is shown in Mean ± Standard deviation

Table 31: Length of Stay with Respect to Diabetes (n=148)

Diabetes	Length of Stay	P-value
Yes	5.08 ± 3.48	0.660
No	5.64 ± 4.51	

Data is shown in Mean ± Standard deviation

Table 32: Length of Stay with Respect to Previous Abdominal Surgery (n=148)

Previous abdominal surgery	Length of Stay	P-value
Yes	5.83 ± 4.68	
No	5.52 ± 4.36	0.711

Data is shown in Mean ± Standard deviation

DISCUSSION

Symptomatic Cholelithiasis:

The incidence of cholelithiasis is approximately 10% in the United States, and 10 to 15% of those patients will become symptomatic.20 The patients usually present with acute, colicky pain in the upper abdomen, typically experienced after fatty meals. In addition, nausea and vomiting can occur. However, some patients only report vague complaints related to the upper right abdomen. Diagnostic work-up consists of laboratory investigations, with special emphasis on bilirubin and alkaline phosphatase and an ultrasound of the abdomen. These investigations lead to the correct diagnosis in almost all cases. Additional examinations, such as computed tomographies (CT scans) or gastroscopies, might be needed in order to rule out other diseases (e.g. acute gastritis, tumour formation). Uncomplicated cholelithiasis can be treated conservatively with painkillers, with an elective laparoscopic cholecystectomy is performed later. When no operation is carried out, the rate of developing complicated cholelithiasis identified in the follow-up of patients with mild symptoms is slightly higher, at up to 3% per year compared to 1 to 2% of patients with asymptomatic stones [27]. If the patient's history (jaundice, acute pancreatitis) and/or the laboratory investigations suggest choledocholithiasis (increased bilirubin or alkaline phosphatase), a preoperative endoscopic retrograde cholangiopancreatography (ERCP) is indicated to clear any stones from the bile ducts and to confirm the diagnosis. If no strong evidence for common bile duct stones is present, such as elevated bilirubin and alkaline phosphatase or dilated intrahepatic bile ducts in the ultrasound, preoperative ERCP is not necessary; it can be performed postoperatively if there is a suspicion of stones remaining in the bile duct [20]. Intravenous cholangiography before surgery to detect choledocholithiasis or abnormal bile duct anatomy has not shown a benefit and is no longer justified [20]. As an alternative to the invasive ERCP process, a magnetic resonance cholangiopancreatography (MRCP) can be performed to investigate the biliary tree. Especially in patients who have had previous upper abdominal surgery, such as Roux-en-Y reconstruction, it might be very difficult or even impossible to perform an ERCP. In these special cases, MRCP can be very helpful. However, MRCP has no therapeutic options.

Acute Calculous Cholecystitis

Acute calculous cholecystitis predominantly occurs as a complication of gallstone disease and typically develops in patients with a history of symptomatic gallstones. In a systematic review, it was seen in 6 to 11% of patients with symptomatic gallstones over a median follow-up period of 7 to 11 years [20].

Definitions

The term cholecystitis refers to inflammation of the gallbladder. It may develop acutely in association with gallstones (acute calculous cholecystitis) or, less often, without gallstones (acalculous cholecystitis). It may also develop over time and be discovered histologically following cholecystectomy (chronic cholecystitis).

Acute Calculous Cholecystitis — A syndrome of right upper quadrant pain, fever, and leukocytosis associated with gallbladder inflammation that is usually related to gallstone disease.

Acalculous Cholecystitis — Acalculous cholecystitis is clinically identical to acute cholecystitis but is not associated with gallstones and usually occurs in critically ill patients. It accounts for approximately 10% of cases of acute cholecystitis and is associated with high morbidity and mortality rates.

Chronic Cholecystitis — This term is used to describe chronic inflammatory cell infiltration of the gallbladder, observed on histopathology. It is almost invariably associated with the presence of gallstones and is thought to be the result of mechanical irritation or recurrent attacks of acute cholecystitis leading to fibrosis and thickening of the gallbladder [1]. Its presence does not correlate with symptoms, since patients with extensive chronic inflammatory cell inflammation may have only minimal symptoms, and there is no evidence that chronic cholecystitis increases the risk of future morbidity [21]. Hence, the clinical significance of this entity is questionable.

Some authors use the phrase 'chronic cholecystitis' when referring to gallbladder dysfunction as a cause of abdominal pain [21]. However, it is more appropriate in this instance to refer to the condition based on the disorder present, such as pain due to gallstone

disease, pain due to biliary dyskinesia (which is attributed to sphincter of Oddi dysfunction), or pain due to functional gallbladder disorder (also called gallbladder dyskinesia).

Pathogenesis of Acute Calculous Cholecystitis:

Acute calculous cholecystitis occurs in the setting of cystic duct obstruction, yet, unlike biliary colic, acute calculous cholecystitis cannot have its development fully explained by cystic duct obstruction alone. Studies suggest that an additional irritant (possibly lysolecithin) is required to develop gallbladder inflammation. Once inflammation of the gallbladder begins, additional inflammatory mediators are released, further propagating gallbladder inflammation. In many patients, infection of the biliary system is also involved in the development of acute calculous cholecystitis.

Studies in animals have demonstrated that ligation of the cystic duct alone does not result in acute calculous cholecystitis [21]. However, acute calculous cholecystitis can be produced by blocking the cystic duct, followed by deliberate irritation of the gallbladder mucosa (either mechanically, with an indwelling catheter, or by the infusion of an irritant). One such irritant used in experimental models, lysolecithin, is produced from lecithin, a normal constituent of bile. The production of lysolecithin from lecithin is catalysed by phospholipase A, which is present in gallbladder mucosa. This enzyme may be released into the gallbladder following trauma to the gallbladder wall from an impacted gallstone. Supporting this hypothesis is the observation that lysolecithin (normally absent in bile) is detectable in gallbladder bile in patients with acute calculous cholecystitis [21].

Inflammatory mediators are released in response to gallbladder inflammation and further propagate the inflammation [21]. Prostaglandins, which are involved in gallbladder contraction and fluid absorption, probably play a central role in this process. In experimental models using human gallbladder tissue, the main prostaglandins synthesised by inflamed human gallbladder microsomes were prostaglandin E2 and 6-keto-prostaglandin F1 alpha, the concentrations of which were increased four times above normal [2]. The prostaglandin hypothesis is supported by the observation that prostaglandin inhibitors relieve biliary colic and can reduce intraluminal cystic pressure.

The infection of bile within the biliary system probably has a role in the development of cholecystitis; however, not all patients with cholecystitis demonstrate this symptom. This observation was supported by a study of 467 subjects from whom bile samples were obtained from the gallbladder and common bile duct for aerobic and anaerobic culture [22]. Patients with a variety of hepatobiliary diseases and a healthy control group were included. Patients with gallstones, acute calculous cholecystitis, and hydropic gallbladder were found to have similar rates of positive cultures in the gallbladder and common bile duct, ranging from 22 to 46%, while cultures were generally sterile in healthy subjects. The main species isolated were Escherichia coli, Enterococcus, Klebsiella, and Enterobacter.

Histologic changes of the gallbladder in acute calculous cholecystitis can range from mild oedema and acute inflammation to necrosis and gangrene. Occasionally, prolonged impaction of a stone in the cystic duct can lead to a distended gallbladder that is filled with colourless, mucoid fluid. This condition, known as a mucocele with white bile (hydrops), is due to the absence of bile entry into the gallbladder and absorption of all of the bilirubin within the gallbladder.

Clinical Manifestations of Acute Calculous Cholecystitis:

The clinical manifestations of acute calculous cholecystitis include prolonged (more than four to six hours), steady, severe right upper quadrant or epigastric pain, fever, abdominal guarding, a positive Murphy's sign, and leukocytosis [26].

History — Patients with acute calculous cholecystitis typically complain of abdominal pain, most commonly in the right upper quadrant or epigastrium. The pain may radiate to the right shoulder or back. Characteristically, acute calculous cholecystitis pain is steady and severe. Associated complaints may include fever, nausea, vomiting, and anorexia. There is often a history of fatty food ingestion one hour or more before the initial onset of pain. The episode of pain is typically prolonged (greater than four to six hours) [26].

Physical examination — Patients with acute calculous cholecystitis usually appear ill, febrile, and tachycardic, and they generally lie still on the examining table because cholecystitis is associated with true local parietal peritoneal inflammation that is aggravated by movement. Abdominal examination usually demonstrates voluntary and involuntary guarding. Patients will frequently have a positive Murphy's sign. Patients with complications may have signs of sepsis (gangrene), generalised peritonitis (perforation), abdominal crepitus (emphysematous cholecystitis), or bowel obstruction (gallstone ileus) [26].

Laboratory Evaluation — Patients typically have a leukocytosis with an increased number of band forms (i.e., a left shift). Elevation in the serum total bilirubin and alkaline phosphatase concentrations are not common in uncomplicated acute cholecystitis since biliary obstruction is limited to the gallbladder; if present, they should raise concerns about complicating conditions such as cholangitis, choledocholithiasis, or Mirizzi syndrome (a gallstone impacted in the distal cystic duct which causes extrinsic compression of the common bile duct). However, there have been reports of mild elevations in serum aminotransferases and amylase, along with hyperbilirubinemia and jaundice, even in the

absence of these complications [22]. These abnormalities may be due to the passage of small stones, sludge, or pus. In patients with emphysematous cholecystitis, mild to moderate unconjugated hyperbilirubinemia may be present because of hemolysis induced by clostridial infection [27].

Diagnosis of Acute Calculous Cholecystitis:

Acute calculous cholecystitis should be suspected in a patient presenting with right upper quadrant or epigastric pain, fever, and a leukocytosis. A positive Murphy's sign supports the diagnosis. However, history, physical examination, and laboratory test findings are not sufficient to establish the diagnosis. Confirmation requires demonstration of gallbladder wall thickening or oedema, a sonographic Murphy's sign, or failure of the gallbladder to fill during cholescintigraphy. In most cases, the diagnosis can be confirmed with an abdominal ultrasound. If the diagnosis remains unclear, cholescintigraphy can be performed [28].

Murphy's Sign — Patients with acute cholecystitis frequently have a positive 'Murphy's sign'. To check for a Murphy's sign, the patient is asked to inspire deeply while the examiner palpates the area of the gallbladder fossa just beneath the liver edge. Deep inspiration causes the gallbladder to descend toward and press against the examining fingers, which in patients with acute calculous cholecystitis commonly leads to increased discomfort and the patient catching his or her breath. In one study, which used cholescintigraphy as the gold standard [28], the sensitivity and specificity of a positive Murphy's sign were 97 and 48% respectively [22], though sensitivity may be diminished in the elderly.

Imaging Studies:

Physical examination alone cannot determine which abdominal viscera is the source of inflammation and pain. Thus, patients presenting with clinical features suggestive of acute cholecystitis should undergo abdominal imaging to confirm the diagnosis. Ultrasonography is usually the first test obtained and can often establish the diagnosis. Nuclear cholescintigraphy may be useful in cases in which the diagnosis remains uncertain after ultrasonography [29].

Ultrasonography — The presence of stones in the gallbladder in the clinical setting of right upper quadrant abdominal pain and fever supports the diagnosis of acute calculous cholecystitis but is not diagnostic. Additional sonographic features include [30]:

- Gallbladder wall thickening (greater than 4 to 5mm) or oedema (double wall sign).
- A 'sonographic Murphy's sign', which is similar to the Murphy's sign elicited during abdominal palpation, except that the positive response is observed during palpation with the ultrasound transducer. This is more accurate than hand palpation because it can confirm that it is indeed the gallbladder that is being pressed by the imaging transducer when the patient catches his or her breath.

Several studies have evaluated the accuracy of ultrasonography in the diagnosis of acute calculous cholecystitis [22-23]. A particularly informative systematic review summarised the results of 30 studies of ultrasonography for gallstones and acute calculous cholecystitis [22]. Adjusted sensitivity and specificity for diagnosis of acute cholecystitis were 88 percent (95% confidence interval (CI) 0.74 to 1.00) and 80 percent (95% CI 0.62 to 0.98), respectively. The sensitivity and specificity of ultrasonography for detection of gallstones are approximately 84 (95% CI 0.76to 0.92) and 99 percent (95% CI 0.97 to 1.00), respectively [31]. Ultrasonography may not detect small stones or sludge, as was illustrated by a study that compared ultrasonography with direct percutaneous mini-endoscopy in patients who had undergone topical gallstone dissolution [22]. Ultrasonography was negative in 12 of 13 patients in whom endoscopy demonstrated 1 to 3mm stones or fragments.

Cholescintigraphy (HIDA Scan) — Cholescintigraphy using 99mTc hepatic iminodiacetic acid (generically referred to as a HIDA scan) is indicated if the diagnosis remains uncertain following ultrasonography [32]. Technetium-labelled hepatic iminodiacetic acid (HIDA) is injected intravenously and is then taken up selectively by hepatocytes and excreted into bile. If the cystic duct is patent, the tracer will enter the gallbladder, leading to its visualisation without the need for concentration. The HIDA scan is also useful for demonstrating patency of the common bile duct and ampulla. Normally, visualisation of contrast within the common bile duct, gallbladder, and small bowel occurs within 30 to 60 minutes. The test is positive if the gallbladder does not visualise. This occurs because of cystic duct obstruction, usually from oedema associated with acute cholecystitis or an obstructing stone. Cholescintigraphy has a sensitivity and specificity for acute cholecystitis of approximately 97 and 90 percent, respectively [33].

Magnetic Resonance Cholangiography — Magnetic resonance cholangiopancreatography (MRCP) is a non-invasive technique for evaluating the intrahepatic and extrahepatic bile ducts. Its role in the diagnosis of acute cholecystitis was evaluated in a series that included 35 patients with symptoms of acute calculous cholecystitis who underwent both ultrasound and MRCP prior to cholecystectomy. MRCP was superior to ultrasound for detecting stones in the cystic duct (sensitivity 100 versus 14%) but was less sensitive than ultrasound for detecting gallbladder wall thickening (sensitivity 69 versus 96%). At the present time, its role in the diagnosis of acute cholecystitis should remain within clinical trials. However, MRCP may be appropriate if there is concern that the patient may have a stone in the common bile duct [34].

Computed Tomography — Abdominal computed tomography (CT) [33-37] is usually unnecessary in the diagnosis of acute calculous cholecystitis, although it can easily demonstrate gallbladder wall oedema associated with acute calculous cholecystitis. Other CT findings include pericholecystic stranding and fluid, and high attenuation bile [22]. However, CT may fail to detect gallstones because many stones are isodense with bile [22]. CT can be useful when complications of acute cholecystitis (such as emphysematous cholecystitis or gallbladder perforation) are suspected or when other diagnoses are being considered.

Complications of Acute Calculous Cholecystitis:

Left untreated, symptoms of cholecystitis may abate within 7 to 10 days. However, complications are common, so patients with suspected acute calculous cholecystitis require definitive treatment (e.g., cholecystectomy). The most common complication is the development of gallbladder gangrene (up to 20% of cases) with subsequent perforation (2% of cases) [22]. Gangrenous cholecystitis is the most common complication of cholecystitis, particularly in older patients, patients with diabetes, or those who delay seeking therapy. The presence of a sepsis-like picture in addition to the other symptoms of cholecystitis suggests the diagnosis, but gangrene may not be suspected preoperatively.

Perforation — Perforation of the gallbladder usually occurs after the development of gangrene. It is often localised, resulting in a pericholecystic abscess. Less commonly, perforation is free into the peritoneum, leading to generalised peritonitis. Such cases are associated with a high mortality rate.

Cholecystoenteric Fistula — A cholecystoenteric fistula may result from perforation of the gallbladder directly into the duodenum or jejunum. Fistula formation is more often due to long-standing pressure necrosis from stones than to acute cholecystitis [22].

Gallstone Ileus — Passage of a gallstone through a cholecystoenteric fistula may lead to the development of mechanical bowel obstruction, usually in the terminal ileum (gallstone ileus) [22].

Emphysematous Cholecystitis — Emphysematous cholecystitis is caused by secondary infection of the gallbladder wall with gas-forming organisms (such as Clostridium welchii). Other organisms that may be isolated include Escherichia coli (15%), staphylococci, streptococci, Pseudomonas, and Klebsiella. Affected patients are often men in their fifth to seventh decades [22], and approximately one-third to one-half have diabetes [22]. Gallstones are present in about one-half of patients.

Treatment of Acute Calculous Cholecystitis

Treatment of cholecystitis depends on the severity of the condition and the presence or absence of complications. Uncomplicated cases can often be treated on an outpatient basis, while complicated cases may necessitate a surgical approach. In patients who are unstable, percutaneous transhepatic cholecystostomy drainage may be appropriate. Antibiotics may be given to manage infection. Definitive therapy involves cholecystectomy or placement of a drainage device; therefore, consultation with a surgeon is warranted. Consultation with a gastroenterologist for consideration of ERCP may also be appropriate if concern exists about choledocholithiasis. Patients admitted for cholecystitis should receive nothing by mouth if the need for surgery is anticipated. However, in uncomplicated cases of cholecystitis, a liquid or low-fat diet may be appropriate until surgery is needed. The decision to continue providing food by mouth or not may also be guided by whether or not the patient is able to tolerate and keep in what he or she takes [38-40].

Initial Therapy and Antibiotic Treatment:

For acute calculous cholecystitis, initial treatment includes bowel rest, intravenous hydration, correction of electrolyte abnormalities, analgesia, and intravenous antibiotics. For mild cases, antibiotic therapy with a single broad-spectrum antibiotic is adequate. Some options include the following [38-42]:

The current Sanford Guide recommendations include piperacillin/tazobactam (Zosyn, 3.375 g IV q6h or 4.5 g IV q8h), ampicillin/sulbactam (Unasyn, 3 g IV q6h), or meropenem (Merrem, 1 g IV q8h). In severe life-threatening cases, the Sanford Guide recommends imipenem/cilastatin (Primaxin, 500 mg IV q6h).

Alternative regimens include a third-generation cephalosporin plus metronidazole (Flagyl, 1 g IV loading dose followed by 500 mg IV q6h).

- Bacteria that are commonly associated with cholecystitis include Escherichia coli, Bacteroides fragilis, Klebsiella, Enterococcus, and Pseudomonas species.
- Emesis can be treated with antiemetics and nasogastric suction.
- Because of the rapid progression of acute acalculous cholecystitis to gangrene and perforation, early recognition and intervention are required.
- Supportive medical care should include restoration of hemodynamic stability and antibiotic coverage for gram-negative enteric flora and anaerobes if biliary tract infection is suspected.
- Daily stimulation of gallbladder contraction with intravenous cholecystokinin (CCK) has been shown by some to effectively prevent the formation of gallbladder sludge in patients receiving total parenteral nutrition (TPN).

Conservative Treatment of Uncomplicated Cholecystitis:

Outpatient treatment may be appropriate for cases of uncomplicated cholecystitis. If a patient can be treated as an outpatient, discharge with antibiotics, appropriate analgesics, and definitive follow-up care. Criteria for outpatient treatment include the following requirements [43-45]:

- Afebrile with stable vital signs
- No evidence of obstruction according to laboratory values
- No evidence of common bile duct obstruction on ultrasonography
- No underlying medical problems, advanced age, pregnancy, or immunocompromised condition
- Adequate analgesia
- Reliable patient with transportation and easy access to a medical facility
- Prompt follow-up care
- The following medications may be appropriate in this setting:
- Prophylactic antibiotic coverage with levofloxacin (Levaquin, 500 mg PO qd) and metronidazole (500 mg PO bid), which should provide coverage against the most common organisms
- Antiemetics, such as oral/rectal promethazine (Phenergan) or prochlorperazine (Compazine), to control nausea and to prevent fluid and electrolyte disorders
- Analgesics, such as oral oxycodone/acetaminophen (Percocet) or oxycodone/acetaminophen (Vicodin)
- Cholecystectomy

Laparoscopic cholecystectomy is the standard of care for the surgical treatment of cholecystitis. Studies have indicated that early laparoscopic cholecystectomy resulted in shorter total hospital stays with no significant difference in conversion rates or complications [42-45]. The ACR 2010 criteria state that laparoscopic cholecystectomy is the primary mode of treatment for acute cholecystitis.

The Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) issued guidelines for the clinical application of laparoscopic biliary tract surgery in 2010. The guidelines include detailed recommendations for making the decision to operate, performing the procedure, and managing postoperative care, with the patient's safety always the primary consideration. Recommendations are as follows [22]:

- Preoperative antibiotics should be considered only to reduce the possibility of wound infection in high-risk patients, and should then limited to one preoperative dose. Intra-operative cholangiography may improve injury recognition and decrease the risk of bile duct injury.
- If bile duct injury occurs, the patient should be referred to an experienced hepatobiliary specialist before any repair is undertaken, unless the primary surgeon has experience with biliary reconstruction.
- For elective laparoscopic cholecystectomy, the rate of conversion from a laparoscopic procedure to an open surgical procedure is approximately 5 percent. The conversion rate for emergency cholecystectomy where perforation or gangrene is present may be as high as 30 percent.
- Although laparoscopic cholecystectomy performed in pregnant women is considered safest during the second trimester, it has been performed successfully during all trimesters.
- Contraindications to laparoscopic cholecystectomy include:
- High risk for general anaesthesia
- Morbid obesity
- Signs of gallbladder perforation, such as abscess, peritonitis, or fistula
- Giant gallstones or suspected malignancy
- End-stage liver disease with portal hypertension and severe coagulopathy

CONCLUSION

The results of this study showed that the decision to perform delayed laparoscopic cholecystectomy in cases of acute calculous cholecystitis results in a decrease in the rates for conversion of the procedure to an open one, as well as low readmission rates and decreased length of stay.

The region of the hepatobiliary system has been earning the respect and fear of surgeons for a long time. The complicated anatomy, the heterogeneity of its anatomical variations, and relatively difficult access all lead to this region being termed by many as the ‘graveyard of surgeons’. The issues become much more complicated in the setting of acute calculous cholecystitis, where an already difficult situation is made more complicated by inflammatory processes and adhesions, together with an increased propensity for bleeding.

This situation led to an initial propagation of the practice of keeping the patient nil by mouth and giving intravenous antibiotics to first settle down the acute event, with surgery performed at a later date, usually six week down the line. Over time, the trend changed with an increase in the rate of cholecystectomies, but, in the cases of acute calculous cholecystitis, the role of laparoscopic cholecystectomy was first questioned then later resolved in favour of laparoscopic cholecystectomy even for simple cholelithiasis [3-4].

The findings of the current research identified that only eight (5.4%) patients were converted to open cholecystectomy. Readmissions accounted for 32 (21.6%) patients, and the mean (SD) length of stay was 5.59 (4.42) with 62 (41.9%) patients experiencing a length of stay greater than 4 days. The mean (SD) operative duration was 107.69 (32.15), with around 106 (71.6%) patients having an operative duration of more than 90 minutes.

Research into the efficacy of delayed laparoscopic cholecystectomy in the setting of acute cholecystitis has also revealed some other interesting findings. A retrospective study that evaluated the advantages and limitations of delayed laparoscopic cholecystectomy (LC) performed for acute calculous cholecystitis in a tertiary centre between January 2003 and December 2012 reported that the conversion rate to open surgery was 5.8%, while 16.4% of patients were readmitted and the mean length of stay was 20.6 days [10]. There were 593 females (55%) in this study, and the mean age was 57 ± 0.6 years [10].

A recent meta-analysis that assessed 244 patients who had undergone delayed laparoscopic cholecystectomy reported that the length of stay was 9 days, the conversion rate to open surgery was 22.1%, and bile duct injury was 0.6% [5]. Moreover, another meta-analysis that assessed a larger number of patients (816 patients treated with delayed laparoscopic cholecystectomy) reported overall length of stay as 8.3 days, conversion to open surgery as 13.1%, and mortality as 0.3% [11]. In 2013, Gutt *et al.*, reported the mean length of stay as 10 days and conversion to open surgery as 10.5% [12]. Thus, previous studies conducted have shown variations in the length of stay and conversion to open surgery among patients who underwent delayed laparoscopic cholecystectomy (LC) to treat acute calculous cholecystitis.

The results obtained from this study demonstrate and confirm that delayed laparoscopic cholecystectomy among patients with acute calculous cholecystitis has a significantly lower chance for conversion to open surgery. This finding is comparable with other findings in the current literature.

Declarations:

I. **Funding:** None

II. **Conflicts of Interest/Competing Interests:** None

III. **Ethics Approval:** Obtained from royal college of surgeon in Ireland (RCSI).

IV. **Consent to Participate:** All participants agreed to participate in the study voluntarily.

V. **Consent for Publication:** We hereby consent to the publication of this research. We understand that this material may be made available to the public and may be subject to sharing and distribution beyond the control of the publisher.

VI. **Availability of Data and Material:** Availability of data and materials is ensured in compliance with institutional and ethical guidelines. Interested parties may obtain access to the data and materials used in this study by contacting the corresponding author.

VII. **Code Availability:** The source code utilized in this study is available upon request from the corresponding author to facilitate reproducibility and further investigation.

VIII. **Authors' Contributions:** YI, FNA conceived the idea of the study. YI, YAA contributed equally to data collection, data analysis. YI, YAA, FNA contributed to manuscript writing and review of the manuscript. All authors approved the manuscript**.**

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PRO FORMA

Clinical outcomes of delayed laparoscopic cholecystectomy in patients with acute calculous cholecystitis

Name: _____ Serial No: _____
Age: _____ Gender: _____
Date: _____ Hospital Reg. No: _____
Body Mass Index (kg/m^2): _____
Hypertension: Yes ☐ No ☐
Diabetes: Yes ☐ No ☐
Previous abdominal surgery: Yes ☐ No ☐
Operative duration: _____ minutes
Length of stay: _____ days
Conversion to Open Cholecystectomy:
Yes ☐ No ☐
Readmissions: Yes ☐ No ☐