Percutaneous cholecystostomy placement in cases non-responsive, or otherwise non-operable acute cholecystitis: a retrospective descriptive and outcome analysis

by

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Declaration:

I, Dr. Karan Gandhi, hereby declare that the research reported in this dissertation is based on my independent work (except where acknowledgements indicate otherwise) and that neither the whole work, nor any part of it has been, is being, or is to be submitted for another degree to any other university.

This work has not been reported or published prior to registration for this degree.

Signed by candidate

Karan Gandhi
Date: 07th February 2020

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As per Form FHS015

Research Protocol – Section C

Human Research Ethics Committee

University of Cape Town

1.1. Introduction

1.1.1. Title

Percutaneous cholecystostomy placement in cases non-responsive or otherwise non-operable acute cholecystitis: a retrospective, descriptive and outcome analysis

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1.2. Purpose of the Study

The primary aim of this research is to demonstrate the safety and efficacy, or lack thereof, of percutaneous cholecystostomy placement as a management option in patients with acute cholecystitis (AC), not suitable for cholecystectomy and not responding to best medical management.

The secondary aim of this research is to investigate the feasibility and complexities of interval cholecystectomy in this cohort of patients, with respect to the conversion rate to open, operating time and performing a subtotal cholecystectomy.

1.3. Background

Acute cholecystitis is a complication of cholelithiasis (gallstones) and one of the most common admission diagnoses in Acute Care Surgery Units. The standard of care, according to the Tokyo Guidelines (1-4), for the management of acute cholecystitis, includes the immediate use of empiric antimicrobial drugs and index-admission laparoscopic cholecystectomy. A (>72 hour) delay between the onset of symptoms and presentation and initiation of medical care, as well as high operative risk patients are the two main reasons for diversion from this protocol of care. In the case of delay, the guidelines suggest the use of interval (six week) cholecystectomy as appropriate care.

Index admission cholecystectomy in the setting of delayed presentation has been associated with increased morbidity. As inflammation of the gallbladder progresses, the tissues become more oedematous, with anatomic distortion and therefore increased difficulty in identifying important structural landmarks during LC. This difficulty increases the risk of operative complications, including bleeding and common bile duct injury, the most feared complication of LC. In addition to this distortion, adjacent surrounding organs may be involved in this inflammatory complex, thereby also being placed at risk of injury during dissection. In such circumstances, alternative methods of controlling disease progression may be necessary.

According to the Tokyo guidelines (1-4), AC can be classified into three grades of severity, namely mild (grade I), moderate (grade II) and severe (grade III). The grading system takes into account clinical and laboratory parameters, with organ dysfunction representing more advanced disease. Percutaneous cholecystostomy tube placement has been described as a method to achieve sepsis control in patients with severe AC, in which case LC may not be safe, owing to operative and high anaesthetic risk. The use of percutaneous cholecystostomy is well established in critically ill patients with acalculous cholecystitis and its safety and efficacy have been reported in many studies (5-11). Early LC has recently been shown to reduce the rate of major complications as compared to PC, even in high risk patients (15)

The management of one subset of patients with acute cholecystitis remains unclear. This group comprises those with delayed presentation, in whom index-admission surgery is not advised, but who subsequently do not respond to best medical therapy. They have traditionally undergone urgent cholecystectomy but suffer higher rates of both morbidity and mortality (12-14).

In the current setting, patients often present with a delay since the onset of symptoms, rendering index-admission cholecystectomy unsafe. This problem is exacerbated by the lack of urgent operating theatre time, often with more urgent cases taking preference, thus delaying operative care beyond what is deemed safe by the Tokyo guidelines. The vast majority of patients are managed by interval cholecystectomy, leaving only the mentioned unresponsive subset. Recent reports have established the safety of the use of percutaneous cholecystostomy tube placement in patient groups that include this subset (severe sepsis, septic shock, local gallbladder rupture, progressive intolerant pain and persistent fever) (5-11).

1.4. Methodology

1.4.1. Study design

An observational research project of cohort study type based on retrospective data collection and analysis.

1.4.2. Study Setting

The current setting refers to the Acute Care Surgery Unit at Groote Schuur Hospital, Cape Town. All patients seen with recent onset (or recurrent) acute right upper quadrant (abdominal) pain, fever, nausea and localized tenderness are subjected to:

- Routine blood investigations (full blood count, urea, creatinine and electrolytes, liver

function tests and serum lipase) and

- Ultrasonographic imaging.

The clinically suspected diagnosis of uncomplicated acute cholecystitis is confirmed by the presence of:

- Leukocytosis,
- Normal renal function,
- Non-elevated serum lipase and
- Gallbladder calculi, with gallbladder wall thickening, pericholecystic fluid and the presence of a sonographic Murphy sign.

These patients are admitted to the unit on intravenous empiric antibiotics and analgesia.

Those that respond to initial medical therapy (relief of pain, normalization of temperature and leukocyte count) are converted to oral antibiotics and discharged with a date for interval cholecystectomy (minimum of six weeks). Some patients that present early (within 72 hours of onset of symptoms) may proceed to expedited index-admission cholecystectomy.

Non-responders to initial therapy (patients with persistent pain, fever and/or raised leukocyte count) are subjected to the placement of percutaneous cholecystostomy tubes. Patients that improve on this therapy retain their drainage tubes for a minimum of 10 days and are subjected to an interval cholecystectomy. Non-responders to tube placement are considered for tube replacement or urgent surgery. Antimicrobial therapy is altered in accordance with sensitivity studies on bile specimens taken at tube placement.

1.5. Characteristics of the Study Population

Participants are to be drawn from patients who have been managed for acute cholecystitis by the Acute Care Surgery Unit at Groote Schuur Hospital, as above.

1.6. Patient selection

The cholecystostomy cohort will include the last 37 patients (up until July 2016) who required the placement of a percutaneous cholecystostomy tube for non-responsiveness to best medical therapy as identified by the records of the Department of Radiology. The arbitrary date of July 2016 is chosen to allow for sufficient time to have passed for an interval cholecystectomy to have been performed. This calculation is based on the Unit's average waiting lists. The initial date will be set by the first person on the list.

1.7. Research Procedures and Data Collection Methods

Data collection will be done in a retrospective manner from the following archives:

- Radiology records
- Ward admission book, ward F25, Groote Schuur Hospital
- Department of Surgery notes and prescription charts in the hospital folders of identified participants
- Laboratory records

Data point values for the following variables will be collected:

- Age
- Gender
- History of diabetes, steroid use, smoking, human immunodeficiency virus infection
- Admission blood pressure, heart rate, temperature, full blood count, urea, creatinine and electrolytes, liver function tests and lipase levels
- Initial sonographic findings (as above)
- All antimicrobial use
- All culture and sensitivity results
- Number of cholecystostomy tube placements for each individual in cholecystostomy cohort
- Mention of dislodgement, bleeding, bile leakage, obstruction, malposition or infection in cholecystostomy cohort
- Duration of tube placement
- Time between index admission and interval cholecystectomy
- Total length of hospital stay (index and subsequent admissions)
- Operative time (interval cholecystectomy)
- Mortality

1.8. Data Safety and Monitoring

Data capture will take place in a data tool, which will take the form of a spreadsheet file and performed by the co-investigators. The computer file will only be available to the principal- and co-investigators. No personally identifiable data will be collected in the data tool. All ages will be changed by an arbitrary numerical value that will only be known to the principal- and co-investigator (e.g. add/ subtract 5 from every patient age). Admission dates and length of stay will, likewise, be altered by a schema only known to the mentioned parties. Gender will

be replaced by sets of arbitrarily chosen strings. All analysis will be performed with the abovementioned changes corrected.

A second copy of the file will be made on a digital versatile disk once a week. These copies will be kept in the archives of the Department of Surgery, where similar records are kept. The final computer file and data analysis notebook will similarly be kept in the mentioned archive for the purposes of retrieval of the data by interested parties who have fulfilled the necessary requirements to gain access to the data.

1.9. Data Analysis

Data analysis is performed using the GraphPad Prism software. (https://www.graphpad.com/scientific-software/prism). Descriptive statistics will include point estimates (mean, median, mode) and measures of dispersion (standard deviation, range, quantiles). Categorical variables will be analyzed by Fisher's exact test, chi-squared test for independence (both with appropriate statistical parameter modification as appropriate) and non-parametric tests. Numerical variables will be analyzed by parametric and non-parametric test as indicated by quantile-quantile plots or by the Kolmogorov-Smirnov test for normal data distribution. A confidence level of 95% will be used and upper and lower bounds will be calculated by the method of bootstrapping. Unless otherwise indicated, a two-tail test hypothesis will be used with an alpha-value of 0.05 as discriminator for rejection of the null-hypothesis.

1.10. Description of Risks and Benefits

This research poses no risk to the participants as all data will be collected in a retrospective manner.

1.11. Informed Consent Process

No specific informed consent will be required due to the observational, retrospective nature of the study.

1.12. Privacy and Confidentiality

See Data Safety and Monitoring above.

1.13. Reimbursement for Participants

Not applicable.

1.14. Emergency Care and Insurance for Research-Related Injuries

Not applicable.

1.15. End of Study

This research project is intended for publication in a peer-reviewed journal. A date for entrance and termination has been stated above, together with detail pertaining to data management.

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2. Literature review

2.1. Literature Search Strategy

A structured literature search was performed, using the PubMed electronic database (www.ncbi.nlm.nih.gov/pubmed). The search thread (*acute cholecystitis*) AND (*percutaneous cholecystostomy*) was used. Selected citations from the 404 articles that this search yielded were further reviewed. In addition, manual searches were performed for specific questions that were raised upon reviewing the literature. Non- English articles, duplicated articles and abstracts of conference proceedings were excluded. A total of 53 articles were included.

2.2. Introduction

Acute calculous cholecystitis (AC) is a complication of cholelithiasis (commonly known as gallstones) and one of the most common emergency surgical presentations. As the name suggests, it is an acute inflammation of the gallbladder, usually caused by an impacted stone in the cystic duct causing persistent obstruction. The bile stasis triggers a release of inflammatory mediators, with subsequent secretion of fluid into the gallbladder lumen- thereby causing further distension and inflammation. This is usually complicated by bacterial superinfection, via translocation from the gastro-intestinal tract. The vicious cycle of inflammation and distension can eventually lead to ischaemia, necrosis and perforation of the gallbladder (1).

Diagnosis is based on clinical, laboratory and imaging parameters (2). Patients typically present with right upper quadrant abdominal pain and associated fever, nausea, anorexia and vomiting. The pain is persistent, as opposed to biliary colic where the pain is intermittent. Abdominal examination elicits localised peritonitis, evidenced by a positive Murphy's sign (arrested inspiration due to tenderness on deep palpation) as the tip of the inflamed gallbladder comes into contact with the abdominal wall. Laboratory investigations usually reveal a neutrophil-predominant leukocytosis, with raised biliary ductal (alkaline phosphatase and gamma glutaryl transferase) enzymes, mostly in the absence of jaundice. The imaging modality of choice is ultrasound, which typically shows a distended, thick- walled gallbladder, pericholecystic fluid and a positive sonographic Murphy's sign, usually with gallstones (1, 3). Gallstone disease in general, and therefore, AC usually affects females more commonly than males (4-6).

According to the Tokyo Guidelines (7-11), the standard of care for the management of acute cholecystitis is the use of empiric antimicrobial drugs and laparoscopic cholecystectomy (LC).

Percutaneous transhepatic gallbladder drainage (PTGBD), otherwise known as percutaneous cholecystostomy (PC), is also described in the Tokyo Guidelines as an alternative to LC for sepsis control, in specific clinical settings of AC (7-9, 12). These include patients who are at high risk for anaesthesia, as well as critically ill patients or patients with severe (Grade III) cholecystitis.

This literature review aims to narrate the history and evolution of acute cholecystitis and its management, which led to the current guidelines. It also aims to describe PC, and its technique, touching on safety, efficacy, complications and the natural history or typical clinical course once PC has been performed.

2.3. History

Dr. John S. Bobbs performed the first cholecystotomy (opening of the gallbladder, as opposed to stoma) on July 15th 1867. This was done inadvertently while he was searching for an ovarian cyst in a young female patient with a four year history of biliary colic. He closed the gall bladder after extracting multiple stones and placed it under the abdominal incision. He termed the procedure 'Lithotomy of the gallbladder.' The patient recovered well and lived longer than her surgeon (13).

Dr. Marion Sims performed the first actual surgical cholecystostomy on April 18th 1878. He sewed an open gallbladder to the corner of an abdominal incision after extracting multiple stones and bile. The patient died 8 days later of massive internal haemorrhage. Theodore Kocher performed the first successful cholecystostomy two months later, in June 1878. After this, cholecystostomy became the standard operation for cholelithiasis (13).

Dr. Carl Langenbuch performed the first successful cholecystectomy on July 15th 1882. He believed that the gallbladder itself produced the stones and that cholecystostomy was only a temporary solution, as the stones recurred. This procedure was met by a lot of controversy over the standard cholecystostomy. Cholecystectomy was, hence, less commonly performed until the early 1900's, when it eventually replaced cholecystostomy as the definitive procedure (13).

The first PC was performed by Elyaderani and Gabriele, in 1979. The patient was a 72 year old female, admitted with obstructive jaundice in the setting of metastatic uterine carcinoma. She had an enlarged gallbladder with a mass in the head of pancreas. Her clinical condition was deteriorating due to sepsis (cholangitis) and she was unfit to tolerate any surgery. PC was hence performed, with pus aspirated from the gallbladder. The procedure was uncomplicated and the patient responded well, showing clinical improvement (14).

Subsequently, PC was performed for AC with similar results (15, 16). Shaver et al further developed the procedure and performed it for patients with AC (17, 18). PC thus became recognised as a management alternative in patients unfit for cholecystectomy.

Laparoscopy as a diagnostic or treatment modality or technique was being investigated since the early 1900's, by a number of scientists. The experiments were initially largely performed on animal models and when this was translated to human patients, very few surgeons adopted or advocated for it. The dogma of 'The bigger the cut, the bigger the surgeon' held very strongly. The technique was accepted earlier by gynaecologists during the 1970's, pioneered by German physician, Kurt Semm. When Semm performed the first laparoscopic appendicectomy in 1982, general surgeons began to pay more attention to laparoscopy, mainly for the threat or fear of losing more work to other physicians (19).

The first laparoscopic cholecystectomy was performed on 12th September 1985, by Prof. Dr. Erich Mühe in Germany. He designed and used an instrument (in collaboration with Hans Frost, who worked for a German manufacturing company), that they called the Gallscope. The Gallscope could accommodate a full diseased gallbladder for delivery, had a valve to maintain pneumoperitoneum and instrument working channels with optics and a light conductor. The procedure was completed within two hours (19).

Despite this apparent brilliance, Prof. Mühe's work was met by strong resistance by the German Surgical Society and he was instead ignored and received strong criticism. He presented his findings on two separate occasions in 1986, but again received only skepticism. He submitted an article of the first LC to the American Journal of Surgery, which was rejected because of his difficulty with English (20, 21).

Laparoscopic cholecystectomy was later performed in France by Philip Mouret, on March 17th 1987, by which time, Dr. Mühe had already performed 94 similar procedures. The patient was a 50 year old female, who was undergoing laparoscopic pelvic adhesiolysis and had symptomatic gallstone disease. The patient requested that her gallbladder be removed and, according to Dr. Mouret, the procedure was performed quite naturally and smoothly. The following day, the patient was found dressed and ready for discharge. She felt so well, that she thought her gallbladder hadn't been removed as promised (20, 22).

Philip Mouret's technique was improved by Prof. Jacques Perrisat in 1988, and popularised since then. By 1993, the National Institutes of Health (NIH) declared it 'the treatment of choice for many patients with cholelithiasis' (23)(NIH consensus conference). By 2014, LC was declared the international gold standard for the treatment of symptomatic gallstones.

It is worth mentioning, that the introduction of laparoscopic cholecystectomy marked a historical turning point for general and laparoscopic/ minimally invasive surgery. The procedure led to an explosion in the entire field of minimally- invasive surgery. Despite initial criticism and resistance, its rapid acceptance by both surgeons and the general population alike is unparalleled by any other surgical procedure in history. Patient demand was the most powerful driving force behind its evolution.

In 1992, Prof. Mühe's work was finally recognised and he received the German Surgical Society Anniversary Award, for 'One of the greatest achievements of German Medicine in recent history.' His contribution was recognised by the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) in 1992, and he was invited to give the Karl Storz lecture on new technology, in San Antonio. He titled his talk, The First Cholecystectomy: Overcoming the Roadblocks on the Road to the' Future.'

In the shadow of all this rapid development of management strategies, surgeons quickly overlooked and forgot about the usefulness of cholecystostomy as an alternative, especially in higher risk patients. Its value as a life-saving option and as a bridge to definitive therapy is quite under-appreciated.

2.4. Percutaneous Cholecystostomy

2.4.1. Description

Percutaneous cholecystostomy involves the placement of a drainage catheter (pigtail) into the gall bladder via skin puncture, strictly observing aseptic precautions. The procedure is performed under image guidance (ultrasound or computerised tomography (CT)) as well as under local anaesthesia and/ or procedural sedation. Fluoroscopy is used to confirm correct catheter position and technical success is defined as visualisation of the pigtail loop in the lumen of the gallbladder (24, 25).

Two approaches are used to access the gallbladder, namely trans-hepatic and trans-peritoneal (26-28). In the trans-hepatic approach, access to the gall bladder is achieved via the bare area of the liver. This is the preferred route, according to published guidelines by the Tokyo group, mainly as it reduces the risk of bile leakage. It has the added benefit of enhanced catheter stability and faster tract maturation, however does carry the risk of other complications such as haemobilia and pneumothorax (28-30). Severe liver disease and coagulopathy are contraindications to using the trans-hepatic approach. Trans-peritoneal access may be difficult in patients with massive ascites or bowel interposed between the gallbladder and abdominal wall (24, 25, 27, 28, 31).

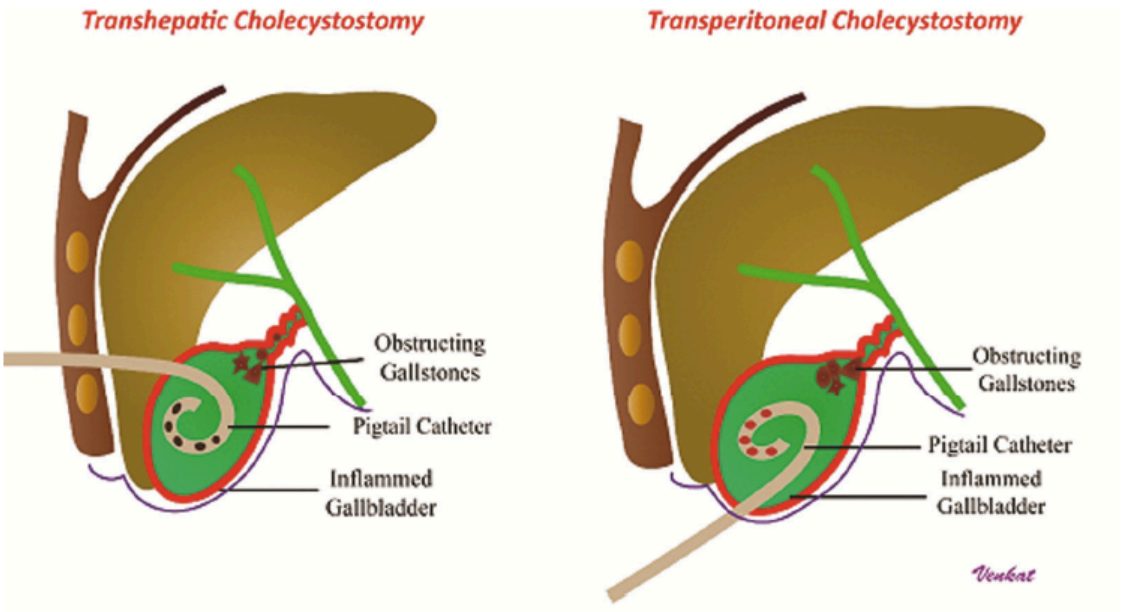

Figure 1: Transhepatic and Transperitoneal approaches to percutaneous cholecystostomy. (32)

2.4.2. Technique

Two techniques of PC have been described, namely the Seldinger technique and the trocar technique. The Seldinger technique involves needle puncture and gallbladder access confirmation by aspiration of bile. Once position is verified by contrast opacification, guidewire placement into the gallbladder follows. Subsequently the catheter is advanced over the guidewire and locked in position (24, 25, 31). The trocar technique involves direct catheter placement into the gallbladder, over a sharp trocar or stylet. This would naturally have the same diameter as the catheter being inserted (24, 25, 31).

The Seldinger technique has the advantage of using a fine needle, thereby reducing the risk of iatrogenic organ perforation and/or injury, while the trocar technique is faster due to the fewer number of manoeuvres. The trocar technique is also associated with a higher risk of bleeding from the liver (24, 25, 31).

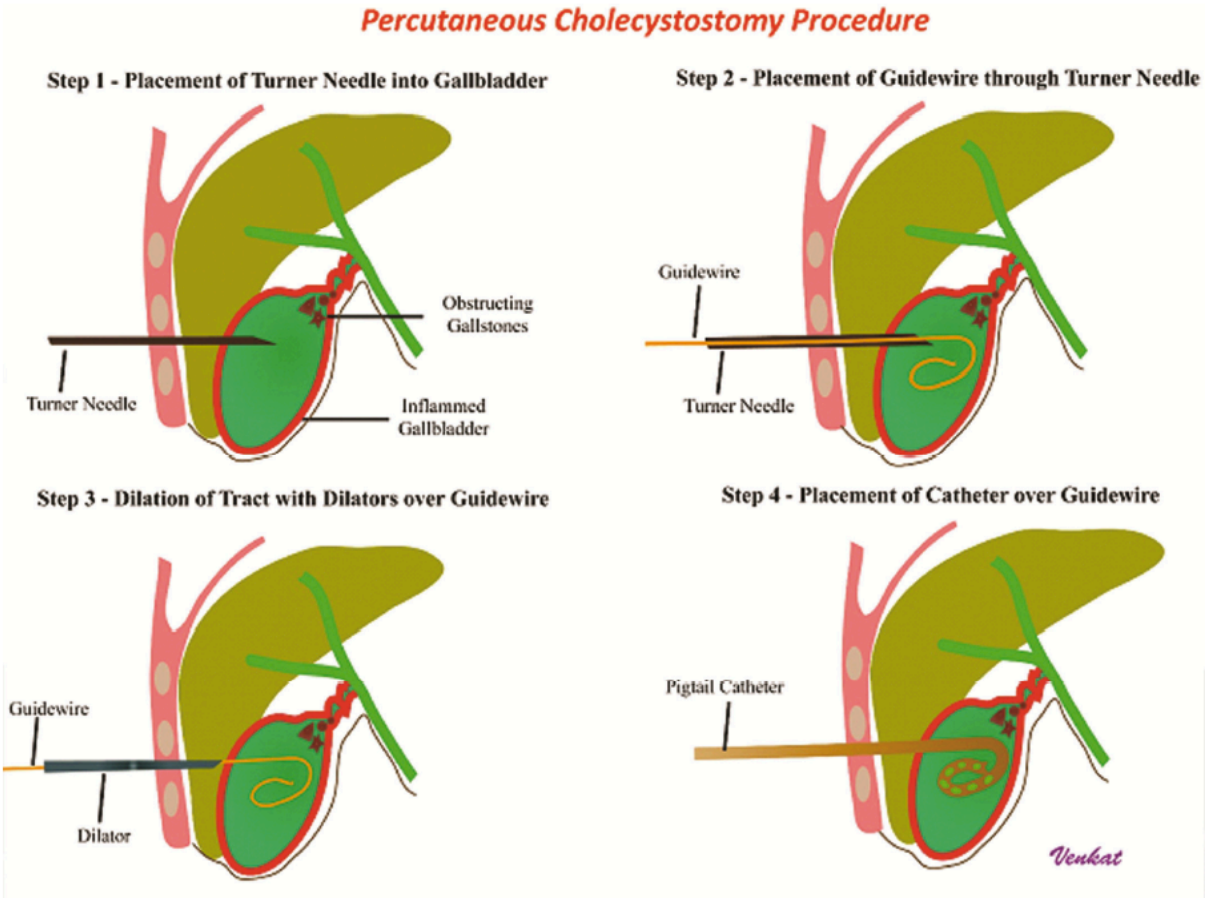

Figure 2: Seldinger technique of performing percutaneous cholecystostomy. (32)

2.4.3. Success rate/ efficacy

The safety (low procedure-related complication rate) and efficacy (positive clinical response) of PC have been described in a number of studies(33-43). Early tube placement has been associated with fewer procedure- related complications and shorter hospital stay (44).

Some studies conclude that PC can be used as definitive treatment for AC, in critically ill or frail, elderly patients who may never be candidates for surgery (36, 37, 43, 45-47). However, when compared in one study to LC (which is the gold standard of treatment), PC has been shown to have little benefit, even in critically ill patients. The authors of this study recommended that PC remain reserved for the specific group of patients who are not surgical candidates (48). Another comparative study performed, with a matched-pair analysis drew similar results and conclusions, stating that the only advantage of PC over LC was the reduced procedure duration (49). In addition to this, the lack of need for a general anaesthetic, in theory, renders PC advantageous.

Technical success rates between 85- 100% are reported in various series (21, 36, 43, 50). Technical failure may be caused by factors that make gallbladder puncture difficult, like porcelain or thick- walled gallbladder. Other factors may include a heavy stone burden, or small gallbladder which does not accommodate the pigtail. Sedation and patient cooperation issues may also contribute to technical failure (24, 31).

Positive clinical response is defined as improvement in patient symptoms, reduction in temperature and reduction in white cell count over 72 hours. A wide range of positive clinical response rates to PC have been reported in the literature (56- 100%). This variation is likely due to differences in patient populations, indications and clinical condition of patients at the time of PC (24).

The value of PC as an alternative to treatment of AC in critically ill or unfit patients cannot be disputed (51). Most studies, however, are retrospective reviews and there remains a gap in the description of PC, its indications, complications and success/failure rates, by way of randomised control trials (21, 41).

2.4.4. Complications/ Mortality

Complications associated with PC can be divided into immediate, early (within the first few days) and delayed/late. Immediate complications include malposition/technical failure, pneumothorax, bile leakage, gallbladder rupture, peritonitis and haemorrhage. Inadvertent injury of an adjacent organ/hollow viscus may be an immediate complication, but might only be recognised within 24-48 hours. Early complications include drain dislodgement and haemobilia. Late complications include drain blockage, dislodgement, secondary sepsis, recurrent cholecystitis, abdominal wall abscess and non-healing of wound/tract (24, 50).

The reported overall procedure-related complication rate of PC is low (< 1%), the most common being catheter dislodgement (21, 24, 29, 50). Pneumothorax is more common when using the transhepatic route, as the puncture site is higher up on the abdominal wall. Haemobilia is rare and bile leakage can range from asymptomatic, to pericholecystic abscess formation, to frank peritonitis requiring surgical intervention. Injury to adjacent organs is extremely rare, owing to imaging techniques and guidance.

When compared with LC, patients who normally undergo PC are generally older, with more chronic illnesses. This relation can probably be attributed to the fact that these patients are less likely to tolerate LC, and hence PC is used for control of sepsis (calculous or acalculous AC). PC is associated with less complications than LC, but patients receiving PC are more likely to die, have increased hospital length of stay and hence increased cost (52). This is probably related to the comorbidities and patient clinical condition, rather than the procedure itself. However, as reported by a recent multicentre randomised superiority trial, LC has been shown to reduce the overall rate of major complications, even in high risk patients, when compared to PC drainage (53).

To highlight this point, as described by a systematic review, the overall procedure- related mortality rate of PC itself is reported to be low (0.36%), with the overall 30- day mortality rate going up to 15.4% (21).

2.5. Clinical course/ Natural history

Once the diagnosis of AC has been made and the decision taken to perform PC, the procedure is performed using one of the techniques described above. Empiric antibiotic treatment is

usually commenced pre- procedure and is guided by local microbiology treatment protocols/ patterns. Gram negative cover is also necessary. Upon puncture of the gallbladder, bile/pus is aspirated and a sample sent for culture. Subsequent antibiotic treatment should be culture-directed (24, 25, 31).

When technical success has been achieved, the drainage catheter is locked in position and the patient is monitored in the radiology suite for any of the immediate complications listed above. Once stable, the patient is transferred to the ward for further monitoring. Routine vital signs are monitored for assessing clinical response. The drainage catheter is flushed twice a day, with 20ml of normal (0.9%) saline, to avoid blockage. Patients are monitored for any features of early complications. If there is no change in clinical condition within 72 hours, it is considered treatment failure and alternative methods of treatment should be considered.

In uncomplicated cases with positive clinical response, patients may be discharged with the drainage catheter in situ. The importance of patient education and drain flushing cannot be overemphasised. There is no consensus for the duration of drainage, but it is based on the development of a mature tract and patency of the cystic duct. Tract maturation can be hindered by a variety of clinical conditions, such as uncontrolled diabetes, malnutrition, steroid therapy, ascites and sepsis (24, 25, 31).

Trans-catheter cholangiography/check-cholecystography is performed at any time between 14-30 days (average tract - maturation duration), to asses cystic duct patency, the presence of stones in the common bile duct and formation of a mature tract. Provided that the cystic duct is patent and the tract matured, the drainage catheter can either be test-clamped, capped or removed. In cases of calculous cholecystitis, stone extraction or lithotripsy options may be considered due to the high rate of recurrence of AC (up to 33%). Recurrent attacks can be managed with repeat PC if necessary. If the patient is for permanent catheter drainage, replacement should be performed at three month intervals (24, 25, 31).

2.6. Question/ Problems

There is no existing South African data on the use of PC for AC (at the time of submission of study protocol). Most literature is from international sources, and local practice is governed by international guidelines. The primary aim of this research is to demonstrate the safety and efficacy, or lack thereof, of percutaneous cholecystostomy placement as a management option

in patients with acute cholecystitis, not suitable for cholecystectomy, or not responding to best medical management.

The secondary aim of this research is to compare these patients to a larger cohort of patients, similarly affected by acute cholecystitis, but who progressed favourably with best medical therapy and were ultimately managed by interval cholecystectomy. Conclusions may be drawn from the results, about the impact of PC on subsequent LC, in terms of procedure difficulties, time and conversion rates to open.

This project may also stimulate consideration of potential for further research on the use of PC for AC in South Africa, and may highlight the potential need for a larger scale, multi- centre trial on the same.

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3. Publication ready original manuscript

Percutaneous cholecystostomy placement in cases non-responsive or otherwise non-operable acute cholecystitis: a retrospective, descriptive and outcome analysis

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Running head: Percutaneous cholecystostomy

Key words: Percutaneous cholecystostomy, Acute Cholecystitis, Calculous cholecystitis, Cholelithiasis, Gallstones, Gallstone disease, Benign biliary disease

Abstract

Background

Acute (calculous) cholecystitis (AC) is an extremely common surgical presentation, managed by cholecystectomy. Percutaneous cholecystostomy (PC) is a potential alternative. However, its safety and efficacy, along with subsequent cholecystectomy, is under-reported in South Africa, where patients often present late and access to emergency operating theatre is constrained. The aim of the study was to demonstrate the outcomes of PC in patients with AC not responding to antimicrobials.

Materials and Methods

A retrospective review of patient records, who underwent PC in Groote Schuur Hospital, Cape Town, between May 2013 and July 2016, was performed. Patients with PC for malignancy or acalculous cholecystitis were excluded. Technical success, clinical response, procedure-related morbidity and mortality were recorded. Interval LC parameters were investigated.

Results

Technical success and clinical improvement was seen in 29 of 37 patients who had PC (78.38%). Malposition (3/37) was the most common complication (8.11%). Two patients required emergency surgery (5.4%), while one tube was dislodged. Median tube placement duration was 25 days (Range 1- 211). 16 patients (43.24%) went on to have LC. Eight required conversion to open surgery (50%). Four had subtotal cholecystectomy (25%). Median surgical time was 130 minutes (Range 60-300). There were no procedure-related mortalities. Eight patients (21.62%) died in the 90- day period following tube insertion.

Conclusions

PC is safe for patients with AC, with high technical success and low complication rate. Subsequent cholecystectomy should be performed, but is usually challenging. The requirement for PC may predict a more complex disease process.

3.1. Introduction

Acute cholecystitis (AC) is a complication of cholelithiasis and one of the most common admission diagnoses in Acute Care Surgery Units. The diagnosis is made according to criteria described in the Tokyo guidelines (4). According to the guidelines, the standard of care for the management of AC includes the immediate use of empiric antimicrobial drugs and index-admission (otherwise known as *hot*) laparoscopic cholecystectomy (LC) (1-3). A (>72 hour) delay between the onset of symptoms and presentation and initiation of medical care, as well as high operative risk patients are the two main reasons for diversion from this protocol of care.

In the case of delay, the guidelines suggest the use of interval (six week) cholecystectomy as appropriate care. High anesthetic risk patients or patients otherwise not suitable to undergo LC may be treated by the placement of percutaneous cholecystostomy (PC) tubes to allow drainage of the gallbladder (1-4). The use of PC is well established in critically ill patients with acalculous cholecystitis and its safety and efficacy have been reported in many studies (5-13).

The management of one subset of patients with acute cholecystitis remains unclear. This group comprises those with delayed presentation, in whom index-admission surgery is not advised, but who subsequently do not respond to best medical therapy. They have traditionally undergone urgent cholecystectomy but suffer higher rates of both morbidity and mortality.

In our setting, patients often present with a delay since the onset of symptoms, rendering index-admission cholecystectomy unsafe. This problem is exacerbated by the lack of access to urgent operating theatre time, thus delaying operative care beyond what is deemed safe by the Tokyo guidelines. The vast majority of patients are managed by interval cholecystectomy, leaving only the mentioned unresponsive subset.

Recent reports have established the safety of the use of PC tube placement in patient groups that include this subset (severe sepsis, septic shock, local gallbladder rupture, progressive intolerant pain and persistent fever)(5, 8-11, 14-19).

Anecdotally, it is generally accepted that laparoscopic cholecystectomy subsequent to PC placement is more difficult and challenging than that following simple AC. However, there is little data to support this entity and the degree of difficulty varies, as does the intra operative decision making.

3.2. Materials and Methods

An observational, descriptive study was performed, based on retrospective data collection and analysis. Radiology records were reviewed, to identify and include potential participants for the study. The cohort included patients who underwent percutaneous cholecystostomy tube placement (PC) for acute calculous cholecystitis, at Groote Schuur Hospital between May 2013 and July 2016. Patients who underwent PC for acalculous cholecystitis, malignancy or gallbladder perforation were excluded. Once the cohort was identified, patient folders were requested from medical records of the hospital for data collection and analysis.

3.2.1. Ethical statement

The study was performed according to a protocol approved by the Human Research Ethics Committee (HREC), of the Health Sciences Faculty, University of Cape Town, HREC Ref: 526/2016.

3.2.2. Data Collection

Data collected included patient demographics, clinical and laboratory parameters on presentation, antibiotic choice, and imaging parameters. Procedure related complications, mortality, duration of tube placement and subsequent cholecystectomy parameters were also recorded and analysed. Data was captured by use of a google form and tabulated in the form of a spreadsheet file. Patient identifiers were removed and each patient was allocated a timestamp (based on time data was captured), to maintain confidentiality.

3.2.3. Statistical Analysis

Data is presented as median ± standard deviation. Statistical analysis was performed using the unpaired Student's *t*-test ($p \leq 0.05$ as significant) (GraphPad Prism software: https://www.graphpad.com/scientific-software/prism).

3.3. Results

A total of 213 patients were treated at Groote Schuur Hospital with acute calculous cholecystitis (AC) between May 2013 and July 2016. Of these, 37 patients underwent percutaneous cholecystostomy (PC), due to failure of empiric antibiotic treatment. The other 176 patients were successfully treated with uncomplicated interval laparoscopic cholecystectomy.

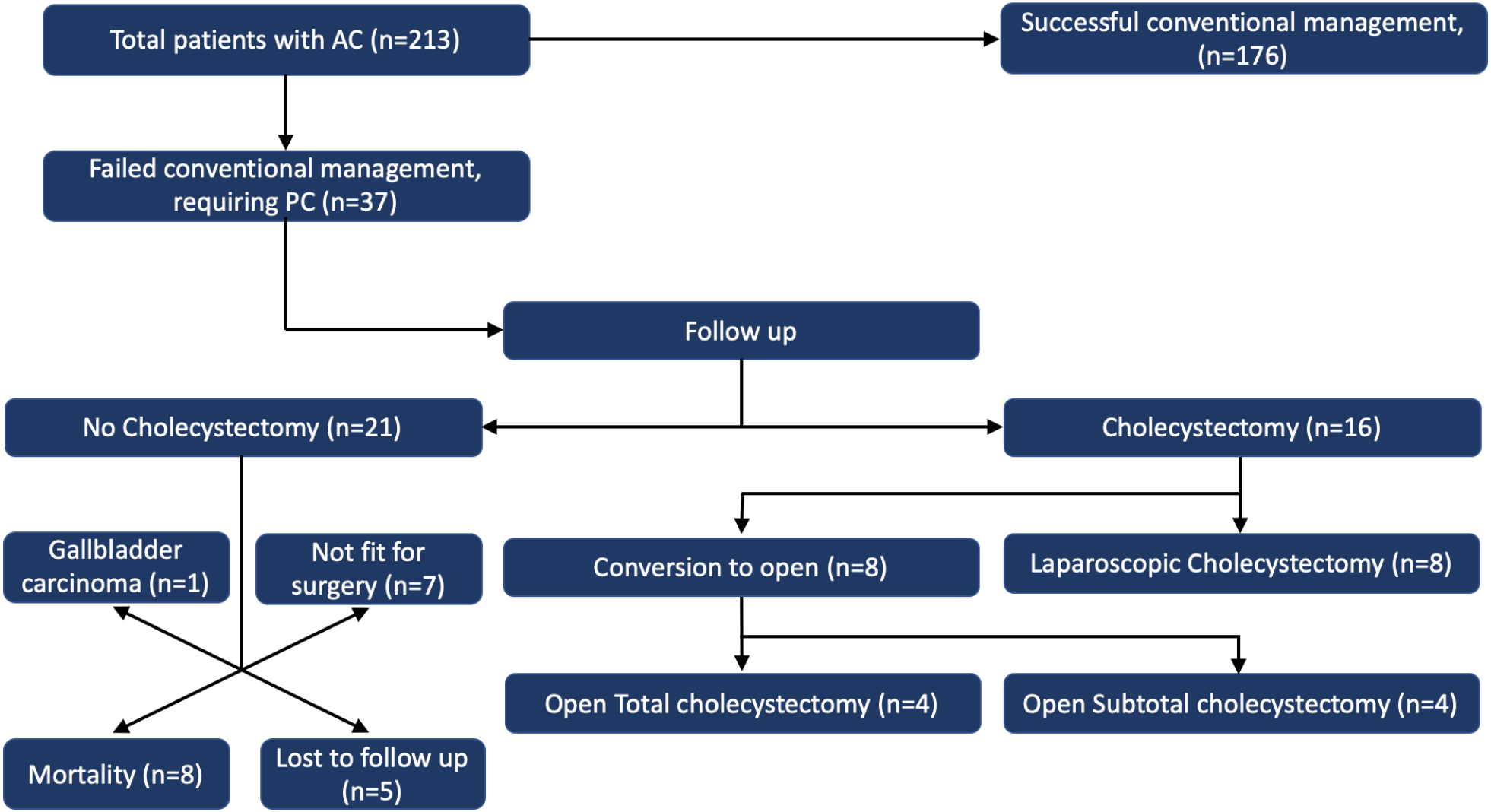

Figure 3: Outcomes of patients with acute cholecystitis (AC) treated at Groote Schuur Hospital between May 2013 and July 2016.

Figure 3 demonstrates the overall clinical progression and outcomes of patients managed over the study period. Data collected for the PC cohort included patient demographics, clinical and laboratory parameters on presentation (Table 1), imaging findings (Table 2) and eventual management.

3.3.1. Basic Patient Characteristics:

3.3.1.1. Demographics

Of the 37 patients, 23 were female and 14 were male. Patient age ranged between 25 and 82 years, with median age 54 years (Figure 4A and Table 1). At a glance, it would appear that females presented across a wider range of age groups compared to males (25- 82 years vs 50-75 years), but this difference was not found to be statistically significant (Figure 4B).

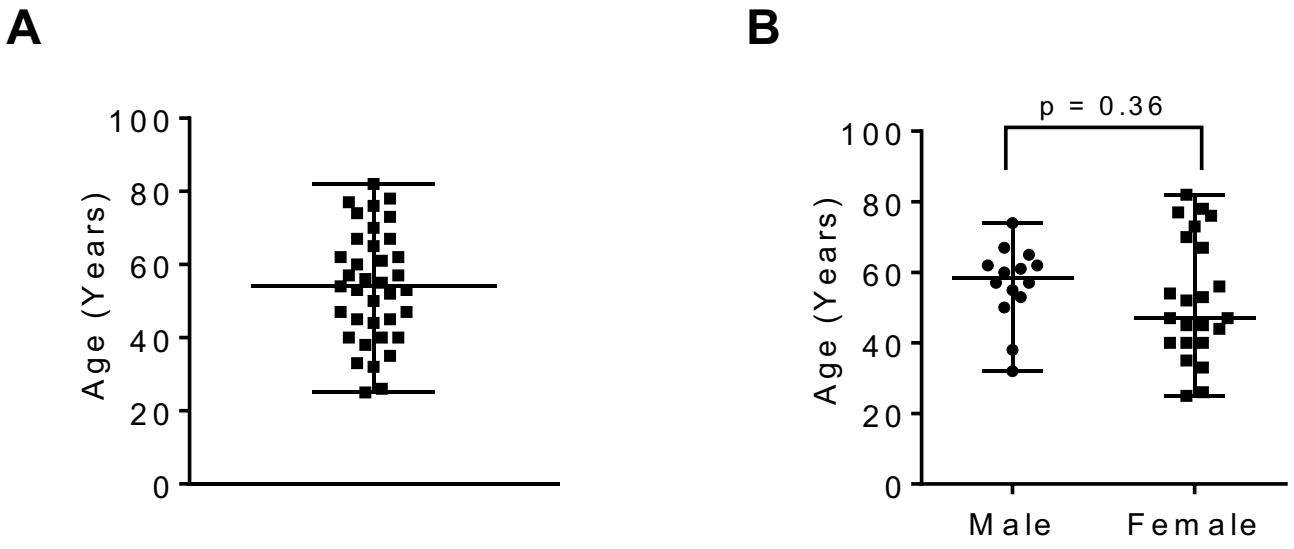

Figure 4: Patient demographics. **A:** Overall age distribution. **B:** Age distribution stratified according to gender. Data presented as median with range. Statistical analysis in **(B)** performed using unpaired Student's *t*-test.

Table 1: Summary of key patient demographics, clinical and laboratory parameters.

Parameter	PC Patients (n = 37)
Age, median (range) ± SD	54 (25-82) ± 15.11
Sex (M:F)	14:23
Body Temp (°C), median (range) ± SD	37.00 (34-40.4) ± 1.46
Blood Pressure (mmHg), median (range) ± SD	
Systolic	120 (60-231) ± 37.57
Diastolic	70 (20-108) ± 37.57
Heart Rate, median (range) ± SD	100 (60-141) ± 20.71
White Cell Count ($\times 10^9$/L), median (range) ± SD	14.04 (1.96-48.82) ± 10.89
Creatinine (µmol/L), median (range) ± SD	81 (40-507) ± 108.63
γGT (U/L), median (range) ± SD	102 (15-1058) ± 262.45
Alkaline Phosphatase, (U/L), median (range) ± SD	126 (37-2323) ± 417.69

3.3.1.2. Clinical and laboratory parameters

At presentation, systolic blood pressure ranged between 60 and 231 mmHg (median 120), with diastolic range between 20 and 108 mmHg (median 70) (Figure 5 and Table 1). Median heart rate was 100 beats per minute (range 60- 141), while median temperature was 37^0C (34.0-40.4). Median white cell count was 14.04 x10^9/L (range 1.96- 48.40) (Figure 5 and Table 1).

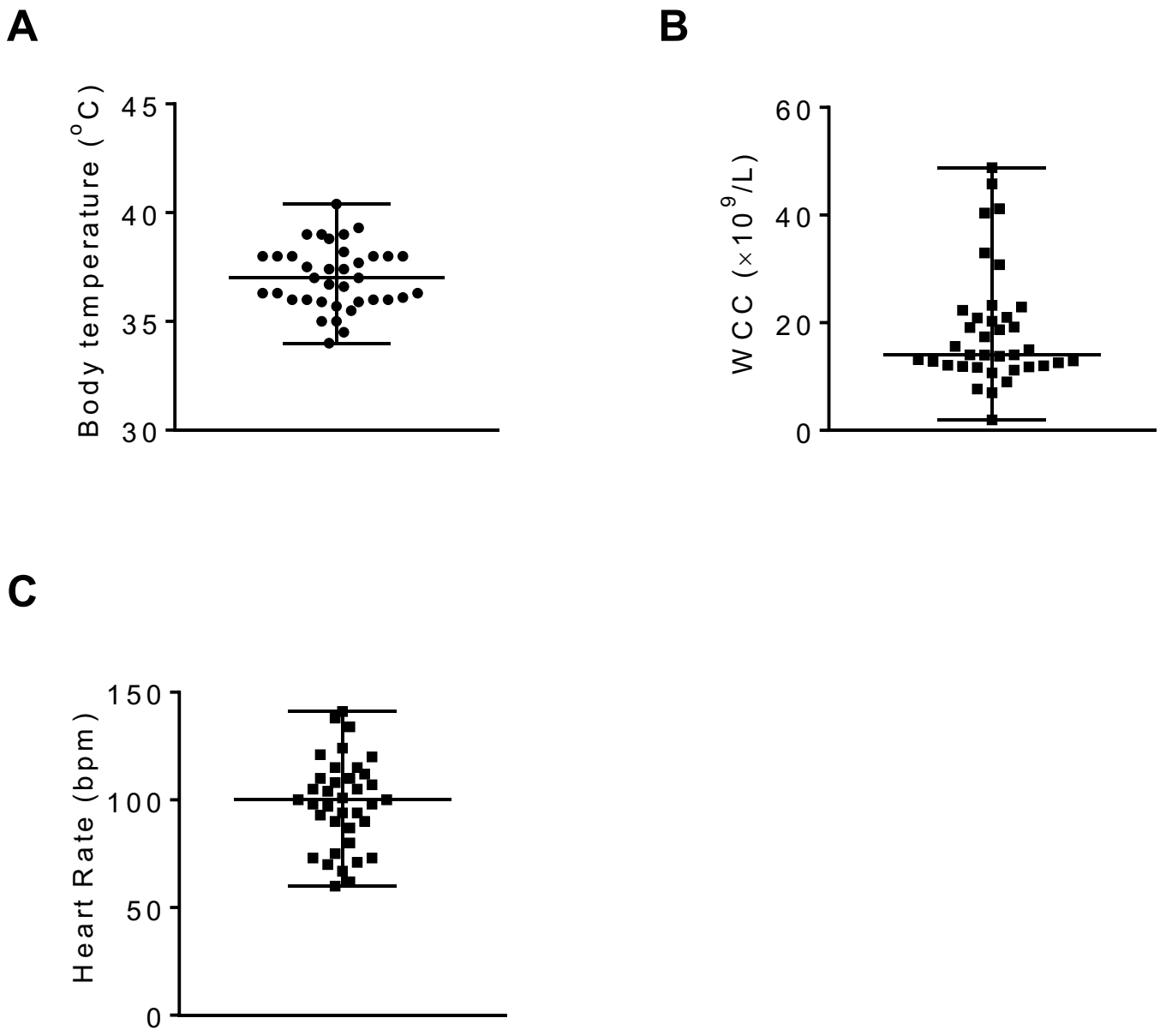

Figure 5: Body temperature **(A),** white cell count (WCC) **(B)** and heart rate (beats per minute-bpm) **(C)** represented as median values with range.

3.3.2. Imaging

On ultrasonography, gallbladder wall thickening was found in 24 patients, while five scans demonstrated no wall thickening. The remaining eight scans had no mention of gallbladder wall thickness. Similarly, pericholecystic fluid was seen on 20 scans, while none was seen on eight scans and nine had no mention of presence or absence of fluid (Table 2). All patients had a positive sonographic Murphy's sign.

Table 2: Summary of ultrasound findings.

Ultrasonography Findings	No. of Patients (n=37)
Gallbladder wall thickening	
Present	24
Absent	5
No mention	8
Pericholecystic fluid	
Present	20
Absent	8
No mention	9

Upon placement of drainage catheter, contrast cholecystogram (fluoroscopy) demonstrated cystic duct occlusion in 29 patients (78.38%). An example of this is demonstrated in Figure 6A below. Eight patients still had a patent cystic duct (21.62%) (Figure 6C). When trans-catheter check cholecystogram was subsequently performed (prior to drain removal), cystic duct patency was demonstrated in 23 patients (62.16%) (Figure 6D). Seven patients never had a check cholecystogram (18.92%), and the remaining seven had no cystic duct patency (Figure 6E). A summary of all these findings is presented in Table 3.

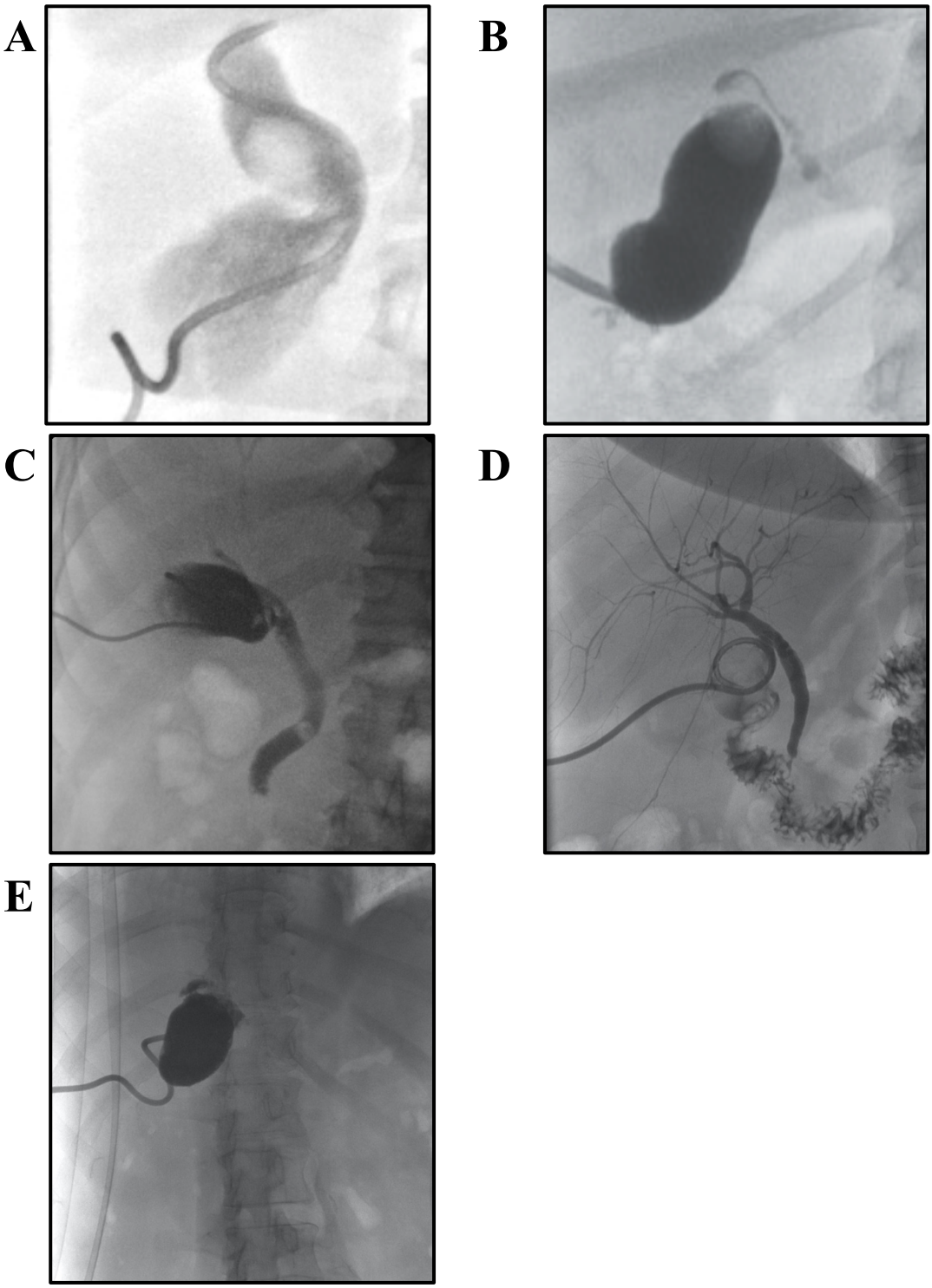

Figure 6A: Insertion cholangiogram demonstrating a large stone in the gallbladder, with occluded cystic duct. **B:** Check cholecystogram for the same patient, demonstrating patent cystic duct, but persistent large stone in the gallbladder. **C:** Insertion cholangiogram demonstrating patent cystic duct with CBD stone. **D:** Check cholecystogram demonstrating patent cystic duct with good flow of contrast into the duodenum. **E:** Check cholecystogram demonstrating persistent occlusion of the cystic duct.

Table 3: Summary of fluoroscopy findings.

Fluoroscopy Findings	No. of Patients (n=37)
Insertion PC	
Cystic duct patent	8
Cystic duct occluded	29
Check cholecystogram	
Cystic duct patent	23
Cystic duct occluded	7
No cholecystogram	7

3.3.3. Complications and outcomes of Percutaneous Cholecystostomy

3.3.3.1. Management

Empiric antibiotic of choice was co-amoxiclav (local preference and protocol), which was administered to 26 of the 37 patients in our cohort (70.27%). For the rest of the patients, in whom amoxiclav was not used for a variety of reasons, local antibiotic stewardship guidelines were used to determine choice of empiric antibiotic. Technical success (correct placement of drainage catheter in the gallbladder lumen with clinical improvement) was achieved in 29 patients (78.38%). Malposition (three) was the most common complication (8.11%) (Figure 8). This was noted at the time of procedure for all patients, upon contrast opacification. These patients all went on to have a second attempt, which was successful. Two patients required emergency surgery (5.5%), while one tube was dislodged (Figure 7). The dislodged drain was not reinserted, as the patient demonstrated clinical improvement after initial drain placement. Median tube placement duration was 25 days (range 0-211).

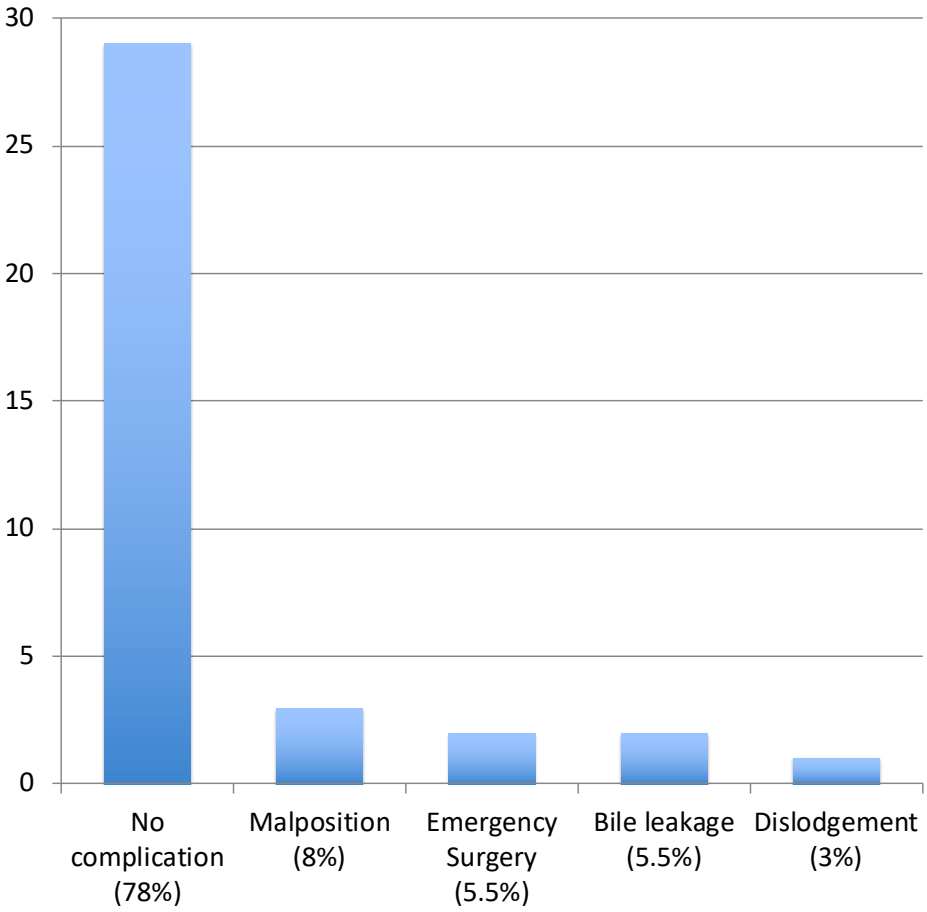

Figure 7: Complications of Percutaneous Cholecystostomy.

Figure 8: Malposition of catheter, demonstrated by free contrast in the peritoneal cavity. The gallbladder in this case was initially accessed and opacified, but subsequent drain placement was incorrect.

There were no procedure-related mortalities, but eight patients (21.62%) died in the 90-day period post tube insertion (Figure 3). Of these eight, three deaths were due to progression of disease (37.5%), while five (62.5%) were due to co-morbid conditions. All three patients that died due to disease progression (worsening sepsis, with organ failure) were from the complication group - two with malposition and one with dislodgement. Of the other five patients that died, two had procedure-related complications, while three had successful PC.

3.3.3.2. Follow up

On follow up, 21 patients (56.76%) did not have definitive surgery (one due to diagnosis of a gallbladder carcinoma, eight due to death, seven due to anaesthetic risk, and five were lost to follow-up) (Figure 3). Of the seven anaesthetic risk patients, two had recurrent symptoms post drain removal, which necessitated second drain placement. The other five patients had no recurrence of symptoms. In the 16 patients who went on to have cholecystectomy (43.24%), high conversion rate (50%) and likelihood of subtotal cholecystectomy (25%) was demonstrated (Figures 3 and 9). The reasons for this high rate were not clear from the operative notes, but are thought to be due to inability to safely proceed with laparoscopic dissection and anatomical identification. Median surgical time was 130 minutes (Range 60- 300). In the cohort of patients who underwent cholecystectomy, median duration between tube placement and surgery was 57 days (Range 0-126 days).

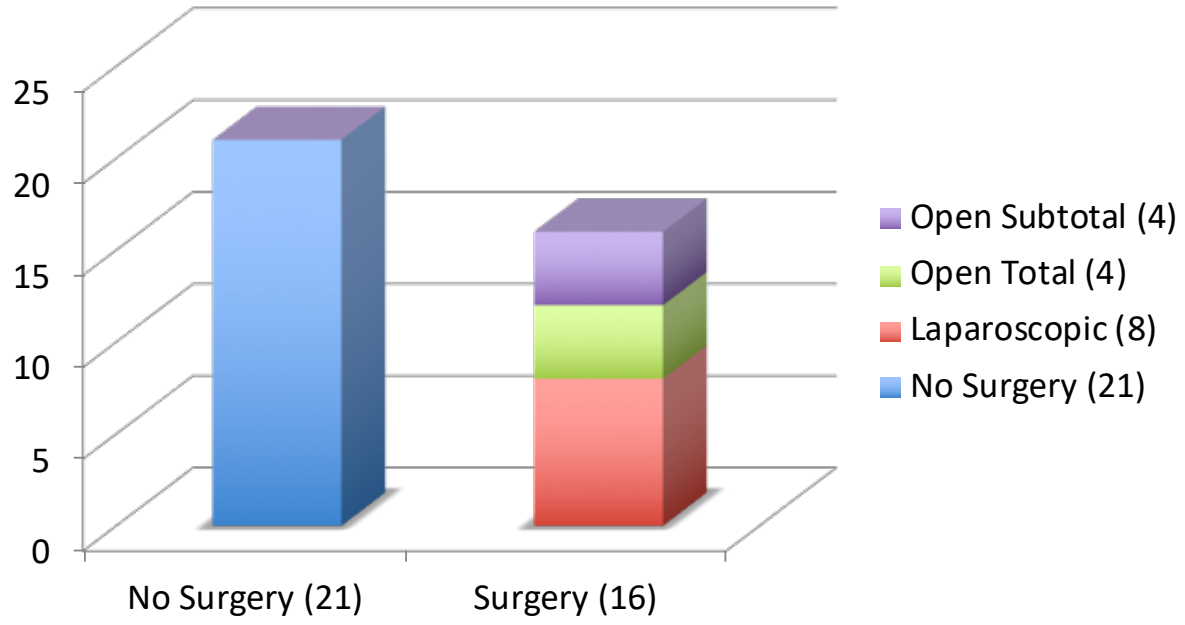

Figure 9: Parameters of interval cholecystectomy.

3.4.Discussion

Acute calculous cholecystitis (AC) can be divided into three severity grades; mild cholecystitis (grade I), moderate cholecystitis (grade II), and severe cholecystitis with organ failure (grade III), based on the Tokyo guidelines (2, 3, 20). It is one of the most common emergency surgical admission diagnoses. For patients that are fit for surgery, expedited index admission laparoscopic cholecystectomy (removal of the gallbladder) is the recommended treatment. In the South African setting however, patients often present late since the onset of symptoms, leading to progressive inflammation, sepsis or septic shock. Under these circumstances, it is thereby unsafe to perform cholecystectomy, as suggested by the Tokyo guidelines. Moreover, patient factors such as comorbidities and immunosuppression, coupled with the lack of access to urgent operating time, further adds to the difficulties in managing AC. Thus, the majority of patients receive interval cholecystectomy, after treatment with empiric antibiotics.

Our study looked at a specific subset of South African patients attending a tertiary level hospital (Groote Schuur Hospital- GSH) with acute calculous cholecystitis, that did not respond to initial treatment with empiric antibiotics. This subset of patients underwent percutaneous cholecystostomy (PC) tube placement in an attempt to achieve source control and thereby treat cholecystitis. The safety of PC as a procedure to treat AC has been reported and established in the elderly and critically ill (15), and in other cohorts (16, 21, 22), but data is lacking in a South African setting.

In our study population, the diagnosis of AC was made using a combination of clinical findings, laboratory parameters and imaging characteristics. Patients included in our study (that had PC catheter placement) presented with a wide range of vital signs. Temperature ranged from hypothermia to pyrexia, blood pressure ranged from hypertension to hypotension and shock and pulse rate ranged from normocardia to tachycardia. These findings are very non-specific and represent a wide spectrum of disease severity, in keeping with the grading system defined by the Tokyo guidelines (2, 3, 20). Owing to the retrospective nature of our study, we did not individually or collectively grade the disease severity in our patient cohort. Moreover, within the confines of the study, our criteria for PC drainage was not based on the clinical severity at presentation, but rather by lack of response to initial empiric antibiotic treatment. Perhaps this may be looked at as a limitation, and a correlation between disease severity and lack of response may be investigated further in a subsequent study. From this data, it is not possible to draw a

conclusion about predicting antibiotic treatment failure based on clinical severity (grade of AC) at presentation. While it is recommended that grade 3 cholecystitis is managed with PC placement as primary therapy, we feel that grade 1 and 2 cholecystitis should only require salvage PC placement in cases of antibiotic treatment failure. Similar comments can be made about the utility of white blood cell count in predicting the need for PC.

Ultrasound findings diagnostic of cholecystitis include gallbladder wall thickening, presence of pericholecystic fluid and a positive sonographic Murphy's sign, elicited using the ultrasound probe (23). Furthermore, the presence of gallstones is mandatory to label it 'calculous' cholecystitis. As reported by Pinto and colleagues, ultrasound remains the investigation of choice for diagnosis of AC (23). All patients in our study had gallstones and a positive sonographic Murphy's sign on ultrasound. However, eight of the 37 ultrasound reports had no mention of wall thickness, while 24 patients had gallbladder wall thickening. The remaining five had wall thickness within normal limits. Similarly, pericholecystic fluid was seen on 20 scans, while none was seen on eight scans and nine had no mention of presence or absence of fluid. Despite these obvious reporting shortfalls, the diagnosis of AC was made with confidence, after consideration of all available information at presentation. The usefulness of ultrasound for the diagnosis of gallstones and AC is unquestionable. While we cannot comment on its use to predict need for PC placement, we can certainly propose that a standardized reporting system be implemented and used, to reduce discrepancies in diagnosis of AC.

Our study period extended over 38 months (between May 2013 and July 2016). During this period, there were a total of 213 patients admitted with AC. Of these, 176 were successfully treated either with hot cholecystectomy, or with empiric antibiotics (co-amoxiclav, based on our institute's practice and policy) and interval cholecystectomy., The remaining 37 patients that did not respond to initial intravenous antibiotic therapy underwent PC tube placement. This demonstrates that a small proportion (17.37%) of all patients admitted with acute calculous cholecystitis actually required PC. This finding is supported in other clinical settings (24), which reported that 26% of AC patients (279/1072) received PC tube placement during the study period from October 2004 through December 2013. Our findings also suggest that conventional therapy for AC is generally successful, as noted for 82.62% of patients in our study. Similarly, (24) also found that ~74% of patients responded to hot cholecystectomy (42%) or antibiotic treatment (32%) as conventional therapy to treat AC.

Of the patients that underwent PC tube placement, 23 were female (62.2%), while the remaining 37.8% were male. This is unlikely to represent lower response to conventional treatment in females, but rather may be explained by the fact that in general, AC is more common in females than in males (25). Indeed, it is well known and documented that gallstone disease occurs more frequently in females than males (26, 27).

The preferred route of placement at our institution is transhepatic, as opposed to transperitoneal, in keeping with the Tokyo guidelines (2, 3, 20, 28). Although bleeding (16, 29) and an increased risk of pneumothorax and subsequent empyema (21) have been documented as complications with the transhepatic route, we did not observe any of these complications during procedure. This observation again, is similar to findings reported in other studies (10, 14). Interestingly, while some literature reports that the transhepatic route is preferred to the transperitoneal route (21, 30, 31), comparative studies have shown similar outcomes between the techniques (10, 29), stating that the choice between the two lies with the operator and on other factors, such as location of the gallbladder and patient body habitus, amongst others (32, 33). We remain neutral on this point as we did not make a comparison between the two approaches.

The procedure was technically successful, with subsequent favourable clinical response post-placement in 78% of patients (29), which is in accordance with success rates reported in other studies (14, 21, 22). Complication rates vary across studies for PC, ranging from 8%-10% (30, 34), to 34% (21). Our results are comparable and fall within this range, as our overall complication rate was about 21.6% with malposition (three patients) being the most common complication followed by two patients needing emergency surgery. Altogether, this highlights that PC tube placement is a safe alternative, with low complication and high success rates, for treating AC in this group of patients.

Upon access of the gallbladder via puncture, fluoroscopy is used to confirm site and correct position for subsequent catheter placement (35-37). Fluoroscopy can also give additional information regarding the status of the biliary ductal system. In this regard, review of fluoroscopy images from radiology records revealed that the cystic duct was occluded in 29 of our 37 patients (78.38%). These findings are in keeping with the pathogenesis of AC and also suggest that persistent cystic duct occlusion may be a predictor of failure of antibiotic treatment, which may necessitate PC placement. Conversely, the remainder of patients

(21.62%) had a patent cystic duct, suggesting that there may have been another cause for antibiotic treatment failure. However, the clinical significance of these points is questionable, as it is not rational or practical to obtain a cholangiogram for every patient presenting with AC, especially in a resource- constrained setting in South Africa. We would therefore recommend that the current, existing treatment guidelines continue to be followed. Similarly, check cholecystogram performed between 10-14 days after PC placement demonstrated cystic duct patency in 62.16% of patients. This is a significant change from the initial 21.62% patency rate. Contrast cholecystography was used to confirm cystic duct patency, prior to catheter removal, and is the standard practice at our institution.

While there were no direct procedure-related mortalities, similar to previous studies (9), we documented eight mortalities (21.62%) in the 90-day period post-tube insertion. However, only three deaths (37.5%) were related to progression of the disease (all from the group that had procedure- related complications) whilst the majority, five deaths (62.5%), were due to co-morbid disease (three of whom had successful PC). In comparison across clinical settings, our reported mortality rate for this study at GSH, South Africa, is fairly comparable to those previously reported at 0-25% (9, 22).

Subsequent to PC placement, 16 patients underwent cholecystectomy. This highlights that PC can serve as an interceptive measure, or bridging therapy, for patients who are deemed surgically unfit at presentation. It also demonstrates that with this management, these patients can undergo an elective procedure later. Support for this is also documented in (14). In our cohort, eight patients (50%) had laparoscopic cholecystectomy, whilst conversion to open cholecystectomy was performed in the remaining 50%, with total and subtotal cholecystectomy representing 25% each. The high conversion rate (50%) is compatible with other studies where it has been documented at 45.5% (14). Once again, as earlier mentioned, data regarding the reason for conversion or subtotal cholecystectomy were not available.

3.4.1. Conclusion

The natural history of untreated AC is progression from inflammation and distension, to infection. Subsequently, as the cycle continues, gallbladder ischemia develops, followed by perforation. This leads to biliary peritonitis, which constitutes a surgical emergency. The same clinical course would ensue in AC not responding to antibiotic treatment. This clinical process has an associated morbidity and eventual mortality, thereby highlighting the need for sepsis

control. PC should, therefore, be reserved as a salvage procedure to achieve this in non-responding patients to antibiotic therapy. Used in this scenario, it may be a life-saving definitive procedure for patients with high-operative risk. One should bear in mind though that the disadvantage of PC is that although the actual inflammation will likely settle, the causative agent (i.e. gallstones) remain and the patient remains at risk of future cholecystitis attacks. Anecdotally, it is accepted that the surgery after PC may be more technically challenging, but there is little data to support this. Furthermore, the degree of difficulty may also vary, as may the eventual procedure or bail-out operation. Our findings suggest similar challenges, but again, the numbers may not be large enough to substantiate this. Further study is required and warranted to provide supporting evidence. With that said, elective cholecystectomy should still be recommended following PC and clinical improvement.

Taken together, while cholecystectomy remains the definitive management for symptomatic gallstones, PC can be viewed as a bridge to this definitive management. Our study, and those of others, have found PC to be safe for high-risk patients with AC, with high technical success and low complication rate. Subsequent cholecystectomy should be recommended, even though the surgery is usually challenging as mentioned above. This may be attempted laparoscopically bearing in mind that the conversion rate to open surgery, with bailout subtotal cholecystectomy, is high. In retrospect, the requirement for PC may serve as a surrogate predictor of AC disease process associated with suboptimal outcome.

Health systems and the referral pathway in South Africa need to improve in order for patients to timeously reach a facility with appropriate levels of care. In addition, the availability of urgent operating theatre time should also be addressed. This would facilitate more patients undergoing early cholecystectomy, in keeping with the standard of care described in the Tokyo guidelines (1-4). Furthermore, early LC performed by a team of experts may help to improve outcomes in patients who present beyond 72 hours, up to a week, thereby reducing the need for bridging therapy with PC.

Further research in the form of a prospective multicentre trial may be considered, to describe PC bridging and interval cholecystectomy, with key emphasis being placed on the surgical difficulties and outcomes of such patients.

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4. Supporting Documents

4.1. List of abbreviations and acronyms

AC	Acute Cholecystitis
CT	Computerised Tomography
γGT	Gamma glutaryl transferase
GSH	Groote Schuur Hospital
HREC	Human Research Ethics Committee
L	Litre
LC	Laparoscopic Cholecystectomy
LFT	Liver function tests
mmHg	Millimetres of mercury
NIH	National Institutes of Health
PC	Percutaneous Cholecystostomy
PTGBD	Percutaneous Transhepatic Gallbladder Drainage
SAGES	Society of American Gastrointestinal and Endoscopic Surgeons
SAJS	South African Journal of Surgery
UCT	University of Cape Town
US	Ultrasound

4.2. Tables and Figures

4.3. INSTRUCTIONS TO AUTHORS- South African Journal of Surgery (SAJS)

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25 July 2016

HREC REF: 526/2016

Dr JH Klopper
Acute Care Surgery
J46, Old Main Building

Dear Dr Klopper

PROJECT TITLE: PERCUTANEOUS CHOLECYSTOSTOMY PLACEMENT IN CASES NON-RESPONSIVE OR OTHERWISE NON- OPERABLE ACUTE CHOLECYSTITUS: A RETROSPECTIVE, DESCRIPTIVE AND OUTCOME ANALYSIS (MMed-candidate-Dr K Gandhi)

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

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

Approval is granted for one year until the 30th July 2017.

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

We acknowledge that the student Dr K Gandhi will also be involved in this study.

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

Please quote the HREC REF in all your correspondence.

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

Yours sincerely

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Principal Investigator to complete the following:

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Date (when submitting this form)	27th January 2020		
HREC REF Number	526/2016	Current Ethics Approval was granted until	30th July 2017
Protocol title	Percutaneous cholecystostomy placement in cases non-responsive or otherwise non-operable acute cholecystitis: a retrospective, descriptive and outcome analysis		
Principal Investigator	Dr Juan H Klopper		
Department / Office Internal Mail Address	juan.klopper@uct.ac.za		
1.1 Does this protocol receive US Federal funding?		☐ Yes	☑ No

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4. Signature

Signature of PI	Dr. Karan Gandhi (GNDKAR001)	Date	27th January 2020