Endoscopic Ultrasound-Guided Gallbladder Drainage With Lumen-Apposing Metal Stents in Comparison to Percutaneous Cholecystostomy for the Non-Surgical Management of Acute Cholecystitis: Systematic Review and Meta-Analysis

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Endoscopic Ultrasound-Guided Gallbladder Drainage with Lumen-Apposing Metal Stents in Comparison to Percutaneous Cholecystostomy for the Non-Surgical Management of Acute Cholecystitis: Systematic Review and Meta-Analysis

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A Thesis in the Field of Biology
for the Degree of Master of Liberal Arts in Extension Studies

Harvard University
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Abstract

Gallstone disease is a widespread medical condition that is associated with high morbidity rates, and often requires surgical intervention (Schirmer, Winters and Edlich). The standard treatment of acute cholecystitis, inflammation of the gallbladder, is laparoscopic cholecystectomy whereby the gallbladder is removed in a mildly invasive surgical procedure. For individuals who are unable to undergo surgery, percutaneous transhepatic drainage of the gallbladder is an alternative option for resolution of cholecystitis. More recently, endoscopic management of acute cholecystitis, such as drainage with metal stents, has emerged as a novel approach that is minimally invasive and associated with a low risk of complications. The objective of this systematic review and meta-analysis is to compare the overall efficacy and safety of endoscopic guided gallbladder (EUS-GB) drainage using all marketed Lumen Apposing Metal Stents (LAMS) with that of percutaneous transhepatic cholecystostomy (PC) in patients that are unable to undergo surgery for treatment of acute cholecystitis.
Dedication

This work is dedicated to my parents Hava and Nuredin Gjata. Not only have they been instrumental in getting me to this point in my life, through unconditional love and support, but they have also been exemplary mentors. They have shown me the beauty of science and medicine, among many other disciplines, and have allowed me to follow my own path. I owe the majority of my accomplishments to them.

My mother, Hava, suffers from gallstones and she is one, among many individuals, an unsuitable candidate for laparoscopic gallbladder removal. Through this work, I hope to possibly provide some answers that might be of benefit to her and others hereafter.
Acknowledgments

I am greatly humbled and deeply honored to have had the opportunity to work with my thesis directors Lina Ginnetti and Dr. Christopher Thompson in drafting this work. I would like to acknowledge and thank them for their generous support and for their extensive knowledge that they have been so kind to share with me in the subject matter, throughout this experience. I am equally honored, and would also like to sincerely thank and acknowledge Dr. James Morris, my thesis advisor, who has been with me since day one of this process. He has provided me with unconditional support, thorough the not-so-straight path, and who has given me the encouragement I needed to cross the finish line. Without the wisdom, support, and direction of these individuals, this project would not have been possible. I am eternally grateful.
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Chapter I

Introduction

Background

Gallstone disease remains one of the leading causes of hospitalization and surgery for gastrointestinal problems (Shaheen et al.; Schirner, Winters and Edlich). Cholecystolithiasis, presence of gallstones in the gallbladder, is responsible for 90-95% of cases of acute calculous cholecystitis—an acute, inflammatory condition of the gallbladder, also known as acute calculous cholecystitis (Kimura et al.). Other, more severe and less common, cases of cholecystitis include acalculous cholecystitis (ACC), gangrenous cholecystitis, xanthogranulomatous cholecystitis, and emphysematous (a.k.a clostridial) cholecystitis. The incidence of acute cholecystitis, presenting with abdominal pain, is over 3 times higher in individuals over 50 at 20.9% versus those who are younger at 6.3% (Telfer et al.).

Without treatment, cases of acute cholecystitis can become increasingly severe, lead to serious complications such as gallbladder perforation, gallbladder empyema (presence of pus in the gallbladder) and may eventually result in death (Allen, Cameron and Loughrey). The standard treatment for acute cholecystitis and any form of symptomatic gallstone disease is to remove the gallbladder by laparoscopic cholecystectomy, a minimally invasive surgical procedure, first performed in 1985 by a German doctor (Walker Reynolds). Like any other surgery, laparoscopic cholecystectomy carries risks; a primary concern being injury to the common bile duct. In a study examining risk factors of laparoscopic cholecystectomy, age and
overall health played a significant role. Systemic complications (e.g. pulmonary embolism, stroke, etc.) were found to be 30% higher for each additional 10 year interval of age and 50% higher in patients with American Society of Anesthesiologists (ASA) score greater than II (patient with mild systemic disease) (Giger et al.).

Due to the variance in severity and the different types of acute cholecystitis a set of grading criteria (Tokyo Guidelines) were established in 2013, after the Tokyo Consensus Meeting in 2007, to provide clinicians with more specific and more accurate diagnosis for affected patients. The guidelines range from Grade I, mild, to Grade III, most severe (see Appendix 1) The severity of acute cholecystitis is graded according to the Tokyo Guidelines. In addition to these guidelines, patients suffering from acute cholecystitis are also classified using the American Society of Anesthesiologist (ASA) Classification, ranging from ASA 1 (healthy patient) to ASA 6 (brain dead patient) (ASA Class; see Appendix 3 for full reference), since laparoscopic cholecystectomy is the standard of care for treatment of acute cholecystitis. This study focuses on patients who are unable to undergo surgery due to their frail state and underlying co-morbidities, therefore they are often classified as least Grade II or greater for acute cholecystitis, and ASA 3 or greater for anesthetic risk.

Percutaneous Cholecystostomy

With the increasing risks of surgery in older patients and those suffering from multiple co-morbidities, laparoscopic cholecystectomy is not for everyone. Individuals who are medically unfit to sustain surgery, have to undergo alternative non-surgical procedures for decompressing the biliary tract. For these patients, the most common form of treatment is percutaneous transhepatic cholecystostomy. PC is performed under ultrasound or CT guidance and it requires the insertion of a plastic tube (catheter) through an opening in the abdomen that
allows the bile to drain into a collection bag outside the body (Mendez, Mancera-Maldonado and Castañeda). PC was first performed in the gallbladder in 1921 (Mendez, Mancera-Maldonado and Castañeda) and has since become the standard non-surgical treatment for acute cholecystitis.

A PC procedure is performed under conscious sedation or general anesthesia. Prior to the procedure a CT scan may be performed to get a better picture of the gallbladder. The insertion of the percutaneous drain can often be carried out at the patient’s bedside, using a single-stick trocar (needle) technique which places the catheter into the gallbladder under ultrasonographic guidance (Lindemann et al.). A small incision is made on the skin of the abdomen. The gallbladder is then punctured after which a needle, guidewire, and dilator are used for proper placement of a single pigtail plastic catheter (see Figure 3. A.) in the gallbladder. Lastly, the plastic catheter is sutured to the skin and protrudes outside the abdomen to drain. The drain is placed such that gravity allows the fluid to drain outside the body. The catheter is then flushed daily with 5–10 ml of sterile saline to avoid occlusion (Akhan, Akınç and Özmen). The catheter is removed once the patient exhibits signs of clinical improvement of acute cholecystitis (see Figure 1). Apart from pigtail catheters, locking loop catheters are also used for percutaneous cholecystostomy. They are used to reduce the risk of dislodgment as catheter dislodgment tends to occur at a high rate after this procedure (Akhan, Akınç and Özmen).

While effective in some, the morbidity rates remain high in elderly and critically ill patients undergoing PC (Hamy et al.; McKay, Abulfaraj and Lipschitz; Klimberg, Hawkins and Vogel), with adverse events such as bile leaks, bleeding, and patients often inadvertently and sometimes intentionally pulling out these tubes (Mendez, Mancera-Maldonado and Castañeda; Irani, Baron, et al.; Andrén-Sandberg et al.).
Endoscopic Gallbladder Drainage

In 2005 Kwan and colleagues developed a new, less invasive, technique of draining the gallbladder through endoscopic guidance by using double pigtail plastic stents (DPPS) (Kwan et al.). The DPPS proved effective in draining the gallbladder (Kwan, Eisendrath, Antaki, Le Moine, & Devière, 2007), however they do require repeat access, and thus are not ideal (Shah et al., 2015). Lumen apposing metal stents have since been designed and are continually being researched for the management of cholecystostomy in critically ill and/or non-surgical candidates in hopes of overcoming the risk of bile leakage, catheter migration, and other complications associated with PC and other stents (i.e. plastic, non-lumen apposing metal stents, etc.) (Yeung and Teoh; Xu et al.).

Lumen Apposing Metal Stents

Currently there are two true LAMS that have been released in different regions globally, the AXIOS™ Stent and Delivery System (Boston Scientific, Natick, MA, USA), and the Niti-S™ SPAXUS™ Stent (Taewoong-Medical Co, Ltd, Gyeonggi-do, Korea). These stents differ slightly in their indications for use, which also vary by country. Alternative endoscopic drains, such as nasocystic catheters or tubular metal stents, are also used by physicians but these stents do not provide the lumen apposition benefits of LAMS. In a study by Teoh and colleagues, ex vivo bench testing of LAMS revealed a significantly higher lumen apposition force (LAF) in the AXIOS™ (Boston Scientific) stent in comparison to other LAMS-like stents, i.e. NAGI™ stent (Taewoong Medical), and a numerically higher difference than the SPAXUS™ LAMS (Taewoong Medical). This mechanical LAF, in addition to the large lumen of LAMS, are considered valuable device characteristics for in providing procedural safety and efficacy. It would be essential to determine the efficacy and safety of LAMS, not only as devices used for
EUS-GB drainage, but also for the design associated benefits that these stents could potentially provide. The large diameter lumen of LAMS provides the added benefit of procedures such as lithotripsy or stone removal to be done through the lumen of the stent, without additional intervention required.

Insertion of a LAMS for cholecystostomy drainage is performed by an experienced endosonographer under EUS guidance. The patient is administered conscious sedation or is placed under monitored anesthesia. Fluoroscopy is used for visualization of the gallbladder with is accessed via a linear endoscope. A needle and guidewire are used to puncture and then looped within the gallbladder respectively. The distal flange of the LAMS is deployed under EUS guidance and the proximal flange is subsequently deployed under endoscopic guidance (Sútil, Betes and Muñoz-Navas).

AXIOS™ Stent and Delivery System

The AXIOS™ Stent and Delivery System (Boston Scientific, Natick, MA, USA) was the first stent and delivery system developed for EUS-guided transluminal drainage of pancreatic pseudocysts. The stent is self-expandable, nitinol-braided and it is fully covered in silicone (see Figure 3. C.). The silicone covering prevents fluid leakage and tissue ingrowth. It allows a physician to use the delivery system (stent is pre-loaded) which deploys a flexible, dual-flange stent into a fluid collection such as a pancreatic pseudocyst or a WON, or a hollow organ such as the gallbladder, so that it may be endoscopically drained into the gastrointestinal tract (Anthony Yuen Teoh et al.; Boston_Scientific). The dual-flanges allow for lumen apposition so that the stent has a smaller change of migration. The stent is 10 mm in length and available in two different lumen diameters, a 10mm and a 15mm, which would be selected based on the fluid to
necrotic debris ratio (i.e. a 10mm for cysts with more fluid content, and 15mm for cysts with greater necrotic debris). In the case of gallbladder drainage, the selection of lumen diameters might also prove beneficial based on the amount and size of stones that are present in the gallbladder. More recently, a newer version of this stent, the AXIOS™ Stent and Electro-Cautery Enhanced Delivery System (see Figure 3. D.), includes an electrocautery tip that penetrates through tissue (e.g. organ wall), and thus eliminates the need for wire exchange and dilation steps (Brückner, Arlt and Hampe). The AXIOS™ has been approved in the United States by the FDA only for endoscopic drainage of symptomatic pancreatic pseudocysts and WON. However, in Europe the AXIOS™ stent has received the CE Mark for pancreatic pseudocysts and for biliary drainage (including the gallbladder) (Dollhopf et al.).

Niti-S™ SPAXUS™ Stent

The Niti-S™ SPAXUS™ Stent (Taewoong-Medical Co, Ltd, Gyeonggi-do, Korea) is an endoscopic device made of flexible nitinol wire covered by a silicone coating to prevent tissue ingrowth and fluid leakage. It has wide, flared ends that fold back upon deployment to hold the two luminal interfaces in apposition and reduce the risk of migration (see Figure 3. B.). It is available in 2cm length, and 8, 10, and 16 mm in diameter (see Table 1). Size selection is determined by the physician based on the size of the collection that needs to be drained. These varying stent sizes could prove beneficial in the presence of gallbladder stones, depending on the size and quantity of stones. The delivery system has an inner and an outer x-ray marker that allow for better visualization under endoscopic view. The Niti-S™ SPAXUS™ Stent has received the CE mark for drainage of a pancreatic pseudocyst or a gallbladder in Europe, and it has also received Health Canada approval for the same indication. However, it does not yet have
FDA approval for any of these indications (Taewoong_Medical; Weilert and Binmoeller).

Percutaneous Drainage Catheters

There are numerous device manufacturers for percutaneous transhepatic cholecystostomy drains. The plastic tubes used for drainage are often pigtail catheters (curled at one end, resembling a pig’s tail) that typically range in size from 6 to 10 French (see Figure 3. A.) (Tsuyuguchi et al.) in thickness along with varying lengths, e.g. 4cm, 7cm, 10cm, etc. The procedure of placing the catheter into the gallbladder lumen is considered technically successful when the pigtail catheter loop is successfully visualized fluoroscopically or by sonography in the gallbladder. The physician obtains a bile sample that is cultured to determine presence of any bacteria since bile should be sterile. If an infection is detected antibiotics are administered.

Systematic Review of the Literature

LAMS carry the advantage of being internal drains when compared to plastic percutaneous cholecystostomy catheters, and thus reduce patient discomfort as well as completely eliminate the risk for a dislodged external drain (J. W. Jang et al.). Additionally, an internal drain typically reduces the need for additional interventions. Prospective trial as well as additional retrospective studies have been carried out to demonstrate successful endoscopic ultrasound guided drainage of the gallbladder with LAMS (Itoi et al.; Kahaleh et al.; de la Serna-Higuera et al.; Walter et al.; Irani, Baron, et al.; Law et al.; Irani, Ngamruengphong, et al.; Dollhopf et al.; A. Y. B. Teoh et al.; Moon et al.). However, very few studies directly compare the outcomes EUS-GBD (using LAMS) with PC for the treatment of acute cholecystitis (Irani, Ngamruengphong, et al.; A. Y. B. Teoh et al.; Tyberg et al.). These studies are not randomized controlled trials, and they do not claim to be systematic. One systematic review, (J. W. Jang et
al.), only looks at EUS-GBD vs. PC with nasobiliary drains, and not LAMS, while another study, (Peñas-Herrero, Serna-Higuera and Perez-Miranda) examines a majority of case reports and not any large studies. Therefore, this study is inclusive of literature that has been systematically selected and analyzed from recent PC and EUS-GBD studies using LAMS.

Primary Objective

The objective of this systematic review and analysis is to compare the overall safety of endoscopic guided gallbladder drainage using all marketed Lumen Apposing Metal Stents with that of percutaneous transhepatic cholecystostomy in patients that are unable to undergo surgery for treatment of acute cholecystitis.

Secondary Objectives

The secondary objectives of this systematic review and analysis will be to also assess technical and clinical procedural efficacy as well as mortality among patients who undergo PC versus EUS-GB drainage procedures with LAMS for the treatment of acute cholecystitis.
Chapter II

Methods

Participants
All patients ages 18 to 95 in eligible studies will be included in this systematic review and meta-analysis without any additional restrictions.

Search Strategy
A full, comprehensive bibliographic electronic search was performed using the following databases: Ovid, Scopus, and PubMed. Studies were limited to a specific time frame beginning from January 1, 2012 to the last search which was conducted in August 2018. The first studies on EUS-GB drainage were published in 2012, therefore primarily, for the purpose of consistency, the limit for both PC and EUS-GB drainage studies was set to begin from January 1st, 2012. The following terms and all their possible combinations were used: “acute”, “calculous”, “acalculous”, “cholecystitis”, “cholecystostomy”, “gallbladder”, “gall bladder”, “drainage”, “percutaneous”, “transluminal”, “transgastric”, “LAMS”, “lumen apposing metal stents”, “AXIOS”, “SPAXUS”, “tube”, “plastic catheter”, “pigtail stent”, “endoscopic ultrasound” “self-expanding metal stent”. No restrictions were placed on study language, as long as English translation of the full article was available. Duplicates citations were removed. The search was limited to human subjects and excluded ex-vivo trials. Further studies were also identified through the reference list in the retrieved articles.
Identification and Selection of Studies

The citations were imported into Endnote and were reviewed by title, abstract, and full manuscript. Screening was independently performed by three individual reviewers (OG, SA, AL), and adjudication was made by discussion among the three reviewers. Since no randomized controlled trials (RCT) data will mostly be captured through retrospective studies, and very few small, prospective studies. Both single center, and multi-center trials were selected.

Methodological criteria for selection and exclusion were recorded (Figure 1.0). A high degree of heterogeneity was expected, therefore no selection criteria or limits were placed on the length of patient follow-up. The following Inclusion and Exclusion criteria were uniformly applied:

**Exclusion criteria:**

1. Case Reports
2. Studies with less than 5 relevant patients
3. Practice guidelines
4. Non-systematic review articles
5. Articles prior to 2012
6. Animal studies, in-vitro studies

**Inclusion criteria:**

1. Controlled Trials
2. Prospective Cohort Studies
3. Retrospective Patient Chart Reviews
4. Case-control studies
5. Case Series (≥ 5 patients)
6. Age (18-95)
7. EUS-GB drainage with LAMS (AXIOSTM, SPAXUSTM)
8. Percutaneous Cholecystostomy
9. Interim analyses of ongoing studies
6. Studies that reported on at least one of the following outcomes:
   a) Clinical Resolution
   b) Complications/Adverse Events

Data Extraction

After identification of all eligible studies, data was extracted into a spreadsheet and MedCalc software was used for further analysis. Basic study characteristics were collected, i.e. study design, sample size, year published, and stent/treatment type for all studies. For comparative cohort studies, the outcomes collected included clinical and technical resolution, complications/adverse events, and mortality. For non-comparative (single-arm) studies, clinical resolution of acute cholecystitis was collected along with complications/adverse events and mortality.

Statistical Analysis

The studies collected for this systematic review were divided into two categories: a) comparative cohort studies that compare PC and EUS-GB drainage head to head., and b) non-comparative (single-arm) studies. Outcomes were evaluated separately for the comparative and non-comparative studies.
Non-Comparative Studies

Due to the lack of randomized controlled trials comparing the outcomes between LAMS and PC for gallbladder drainage, and due to a mixed variety of study designs among the selected non-comparative studies, it was unfeasible to conduct a meta-analysis to compare the gallbladder drainage modalities introduced in this review, therefore only a descriptive review is provided for the non-comparative studies. Safety, efficacy, and any other outcomes, unless otherwise noted, were analyzed using descriptive statistics, i.e. counts and mean values. To estimate outcome measures between the PC and EUS-GB drainage procedure for non-comparative publications, raw counts were pooled from each study.

Comparative Studies

A random effects meta-analysis was performed amongst the comparative studies to evaluate any possible differences between the drainage methods. Some heterogeneity was identified between the comparative studies included in this analysis, primarily in the clinical success outcomes, nevertheless the overall heterogeneity was not significant. However, none of these comparative studies were large enough to perform a sensitivity analysis. To assess the methodological quality of the comparative studies the Methodological Index for Non-Randomized Studies (MINORS) was utilized since none of these studies were randomized controlled trials. A p-value of less than 0.05 was considered statistically significant.
Chapter III

Results

Characteristics of Selected Studies

Forty-one total studies are described in this systematic review and meta-analysis, including three comparative, two arm, studies, and thirty-eight non-comparative studies (non-comparative between PC and EUS-GB drainage with LAMS), with a grand total of 3,645 patients (442 LAMS, 3,230 PC). The comparative studies include a total of 363 patients (146 LAMS and 217 PC) and 3,309 total patients are included in the non-comparative studies (296 LAMS and 3013 PC). The majority of studies, thirty-five, are retrospective, single center, reviews of patient medical charts and only six other studies had retrospectively collected data from multiple centers; all of which report on data collected by proper methodological means. In this review, there is only a single prospective, multi-center trial (Anthony Y Teoh et al.) with a total of 17 patients. Additionally, there are two prospective single center trials (Walter et al.; Cho, Lee, et al.) with 30 and 20 patients respectively, for a grand total of 67 patients from prospective studies. To date, no randomized, controlled studies have been executed to compare clinical outcomes between PC and EUS-GB drainage further with LAMS, therefore all the articles included in this review will be classified as evidence of Grade C (refer to Appendix 1. for grading criteria).

Patients presenting with acute cholecystitis who are not surgical candidates and do not immediately forgo laparoscopic or open cholecystectomy are typically in critical medical condition and often treated in the ICU. Several studies (22 (53.6%)) report on the management of
acute cholecystitis in patients that are being treated in the ICU. Overall, 7 (17.07%) of studies mention treating ICU patients whose primary reason for admission in the ICU was not because of the acute cholecystitis diagnosis, but due to another co-morbidity. In regards to severity of acute cholecystitis and anesthetic risk, 35 (85.37%) articles report on ASA score and/or Tokyo Guidelines grading criteria; ASA ranging from class 2-5 and Tokyo Guidelines grading criteria from 1 to 3. In the two-arm studies, Tyberg at al does not report on acute cholecystitis grading criteria nor ASA class (Tyberg et al.). Irani et al includes patients of all three Grades of acute cholecystitis as well as ASA class 4 and 5 (Irani, Ngamruengphong, et al.). Teoh et al only included patients with Grade III acute cholecystitis and ASA class of 1-4, with the greatest number of patients being in ASA class 3.

Age of subjects was not assessed for the non-comparative studies as there was great variability in reported data, from non-reported age to either a range or average age. In the comparative studies, Teoh at al only included patients aged 80 and above, with an average age of 82.7 years in the EUS-GB drainage with LAMS, and 81.2 average in the percutaneous drainage group. Tyberg et al reports on an average age of 74 years for the LAMS drainage group and 74.37 years for the PC group with no statistical difference in age. Irani et al reports on patients with average age of 65 years in the LAMS drainage group and an average of 75 years of age in the PC drainage group with a non-statistical trend towards younger patients.

Acute Cholecystitis Prevalence Rates

The selected studies included patients with both calculous and acalculous as well as gangrenous cholecystitis patients. Calculous cholecystitis presents with stones in the gallbladder where as acalculous cholecystitis lacks the presence of stones. Acalculous cholecystitis accounts for about (10%) of all acute cholecystitis cases. In this systematic review and meta-analysis, of
the 41 studies included 30 (73.17%) mention either the presence of stones, or that patients were diagnosed with calculous cholecystitis. Cases of acalculous cholecystitis were reported on 10 (23.39%) of the studies included in this review. Gangrenous cholecystitis is a serious complication of acute cholecystitis arising from tension on the gallbladder wall, and presents with necrosis of the gallbladder wall tissue (Chaudhry et al.). Gallbladder gangrene cases were reported in 4 (9.76%) studies.

**Procedure and Outcome Variables for Comparative Studies**

Three studies, (Irani, Ngamruengphong, et al.; A. Y. B. Teoh et al.; Tyberg et al.), directly compared outcomes between percutaneous cholecystostomy and EUS-GB cholecystostomy for the treatment of acute cholecystitis. Using the MINORS scale (see Appendix 2) the Irani et al publication received an overall score of 20, Teoh et al received a score of 21, and the Tyberg et al study received a score of 19. All scores were out of 24 points total.

**Technical Outcomes of Cholecystostomy**

Technical success defined predominantly as ‘successful placement of drainage device’ was collected only in the two arm studies. Due to the different technique of device placement between EUS-guided stent placement and percutaneous drainage placement, it might be more precise to compare technical success outcomes only from studies that directly compared the two procedures together versus studies that report on each procedure independently. By doing so, the definition of technical success is somewhat standardized for the two procedures in each individual study, slightly reducing the heterogeneity between studies.

All three of the comparative studies report on technical outcomes. The total number of patients that had successful technical placement of the drainage device was 141 out of 146 total
patients (96.58%; three publications) in those that had EUS-GB drainage with LAMS and 216 out of 217 total patients (99.54%; three publications) who received PC drains for acute cholecystitis treatment. There was no significant difference in the technical success outcome between PC versus EUS-GB cholecystostomy with LAMS (OR 4.69, CI 0.91 to 24.12, \(p=0.0645\)).

Clinical Success Post Cholecystostomy

Clinical success is reported in all three of the comparative studies. ‘Resolution of acute cholecystitis symptoms’ post stent or catheter placement procedure for gallbladder drainage is primarily the definition of clinical success seen across all of these three studies. Clinically meaningful resolution was also indicated by radiographic imaging, by a reduction in white blood cell (WBC) count, and other laboratory findings. In comparing clinical resolution across these three studies and how it is defined by each study, some heterogeneity is obvious among the clinical success outcomes (see Table 4).

The total number of patients that experienced successful resolution of acute cholecystitis after the stent or catheter placement was 110 out of 146 total patients (75.34%; three publications) in those who had EUS-guided gallbladder drainage with LAMS and 194 out of 217 total patients (89.40%; three publications) who received PC drains for acute cholecystitis treatment. Clinically successful resolution of the acute cholecystitis showed no statistically significant difference among patients who received PC as treatment for acute cholecystitis in comparison to patients who received EUS-GB cholecystostomy with LAMS (OR 2.59, CI 0.39 to 17.42, \(p=0.3264\)).
Complications Post Cholecystostomy

Complications were defined in only two of the three comparative studies, with apparent heterogeneity in those two studies (see Table 4). Complications are recorded throughout the study, mainly during follow-up time after a cholecystostomy procedure. The follow-up times varied in these publications with the average follow-up times ranging from 133 days to 215 days in the EUS-GB drainage with LAMS group, and 213-834 days in the PC group. In the PC group, the mean days to follow up were 213 days, 265 days and 834 days. The 834 days of follow up for this group is certainly an outlier. *Teoh et al* reports on a very long follow up period for the PC group of 834 days, due to having started enrolling PC patients much earlier in the study than patients who received EUS-GB drainage with LAMS. To account for the much longer follow-up period and to avoid any bias in the reported complication rates towards the PC group, *Teoh at al* conducted a Cox proportional hazards regression analysis for the temporal variables. In their analysis, regardless of the time to follow-up, patients who received a percutaneous drain for acute cholecystitis management, were five times as likely to experience a complication than those patients who were treated with EUS-GB drainage with LAMS. They attribute this likelihood to the percutaneous drain, which requires regular maintenance and is often associated with complications including but not limited to frequent catheter dislodgments.

The overall complications that occurred in the EUS-GB drainage with LAMS group were 36 in a total of 146 subjects (26.66%; all three studies). In the percutaneous drainage group, a total of 82 complications occurred in 217 patients (37.79%; all three studies). The patients treated using EUS-GB drainage with LAMS experienced significantly less adverse events than the patients treated with PC for management of acute cholecystitis (OR 3.44, CI 0.91 to 24.12, \( p=0.0006 \)). The highest reported complication in the percutaneous drainage group was drain
dislodgement. The overall dislodgement rate among these three studies was 25 (11.52%) among all patients who were treated with a percutaneous catheter for drainage. Irani et al only reported drain dislodgement rates for patients that experienced re-occurrence of cholecystitis as a result of the dislodgment. Drain obstruction was the second most common complication among patients receiving acute cholecystitis treatment with a percutaneous drain.

Two of the three comparative studies had no patients who proceed to cholecystectomy post cholecystostomy (A. Y. B. Teoh et al.; Irani, Ngamruengphong, et al.). This highlights the severity of overall health for patients included in this analysis, as many patients who are initially unable to undergo laparoscopic cholecystectomy are treated with cholecystostomy as a bridge procedure to eventual surgical removal of the gallbladder.

Mortality Post Cholecystostomy

Mortality was captured from all three comparative studies with apparent heterogeneity. Thirty-day mortality and procedure related mortality were both recorded. Tyberg et al only reported on ‘death during hospitalization from sepsis’. Irani et al does not define mortality, however they report on ‘deaths’ and ‘unrelated’ deaths. Overall mortality rates were 6 patients in the EUS-GB drainage with LAMS group (4.11%) and 8 patients in the percutaneous drainage group (3.69%) with no statistical significance (OR 1.13, CI 0.16 to 8.18, p=0.9063).

Causes of death included, peritonitis, pneumonia, sepsis, acute coronary syndrome, bile leak, and sepsis. The only cause of death with a frequency of more than one per study was sepsis. Among the three studies, a total of 10 (2.75%) subjects died due to sepsis, with 7 deaths in the percutaneous drainage group (3.23%) and 3 deaths in the EUS-GB drainage with LAMS group (2.05%). There was no correlation in any of the other reported causes of death.
Procedure and Outcome Variables for Non-Comparative Studies

Technical Success of Cholecystostomy

Technical success was not collected for the non-comparative studies. Many studies did not report on the technical success of the drainage procedure. In addition, due to the different technique of device placement between EUS-guided stent placement and percutaneous catheter placement, it was decided to only collect technical success from comparative studies, in attempt to reduce any inadvertent bias in the reported outcomes.

Clinical Success Post Cholecystostomy

Clinical success was defined predominantly as resolution of symptoms of acute cholecystitis, with some studies also relying on laboratory markers and imaging for determining clinically significant resolution. Overall 225 (83.03%) patients treated with EUS-GB drainage with LAMS achieved clinical resolution. Among the studies reporting on PC for management of cholecystitis, 1,923 (83.79%) patients achieved clinical resolution post the drainage procedure. Varying means of capturing re-occurrence rates for acute cholecystitis were reported across studies.

Complications Post Cholecystostomy

In an attempt to reduce bias, only procedure and/or device related complication rates were collected. This was due to the fact that many studies differ in their reporting of outcomes, as in some report only procedure/device related complications, and others report all complications. Definitions of complications also differed across studies.
Overall there were 31 (10.47%) reported complication in patients who received EUS-GB drainage with LAMS for the treatment of acute cholecystitis. The complication with the highest frequency reported was bleeding at a rate of 8 (2.70%) out of a total of 296 patients. The second most common complication was re-occurrence of acute cholecystitis which was observed in 4 patients out of a total of 265 (1.5%) patients.

In the PC treatment group, there were a total of 303 (10.06%) complications. Just as in the comparative studies, the most commonly reported complication was dislodgment of the percutaneous catheter, which was reported in 19 of 26 studies (73.08%) with rates as high as 12.27% (Mizrahi et al.). A total number of dislodgement events was not captured as many studies reported on dislodgment as an event, but not the total number of cases/occurrences. Due to the high rate of dislodgments in the PC group there was also a higher reported rate of re-interventions. However, the rate of re-interventions was not collected for this review due to the poor quality in the reported data of re-interventions, making it difficult to analyze.

The second most commonly observed adverse event was bile leak with or without peritonitis, which was observed in 46 total patients across all 26 non-comparative studies reporting on the treatment of acute cholecystitis with PC procedure.

Mortality Post Cholecystostomy

In the non-comparative studies, only in-hospital and 30-day mortality were extracted from the literature, primarily because these time periods most accurately capture intraprocedural mortality (Dewhurst et al.), as well as to reduce bias due to studies either reporting only related or non-related mortality, and/or mortality collected with no specific temporal restrictions.
The overall reported mortality in the PC treatment group was 153 (5.61%) out of a total of 2,725 patients. Mortality was most often reported as a consequence of sepsis and multi-organ failure. In the EUS-GB drainage with LAMS group, the mortality rate was 13 (10.40%) deaths out of a total of 125 patients, with most deaths reported as a result of multiple co-morbidities, overall health, and multi-organ failure.
Chapter IV
Discussion

In the present systematic review and meta-analysis, the primary objective was to compare the overall safety between gallbladder drainage using percutaneous drainage catheters, versus the EUS-guided gallbladder drainage technique using LAMS by analyzing post-procedural outcomes, namely complications and mortality. To date, no randomized, controlled studies have been executed to compare clinical outcomes between PC and EUS-GB drainage further with LAMS further highlighting the significance of this systematic review and meta-analysis.

The overall rate of complications was 10.47% in studies that only examined the performance of LAMS for EUS-GB drainage, and 10.06% in studies that only reported on outcomes of PC treatment for acute cholecystitis. In the two arm studies comparing both drainage techniques, there was no statistical difference in the rate of mortality (4.11% for EUS-GBD with LAMS versus 3.69% for PC, \( p=0.9063 \)) post procedure, however there was a statistically significant lower rate of complications (24.66% for EUS-GBD with LAMS versus 37.79% for PC, \( p=0.0006 \)). As most complications in the PC group were due to catheter dislodgement it is not surprising to see the significant difference in complications. An internal drain, eliminates the chance of dislodgement associated with external drains. Additionally, an internal drain typically reduces the need for additional interventions, however this outcome was not analyzed as part of this study due to great variability across studies. Lower morbidity and fewer additional interventions might very likely translate to shorter hospital stays.
The secondary aim of this study was to determine the clinical and technical efficacy of cholecystostomy between drainage with a percutaneous catheter versus EUS-guided gallbladder drainage with LAMS. The meta-analysis of the two-arm studies performed revealed no statistical difference between these outcomes. However, it is essential to highlight the high heterogeneity among in clinical success outcomes in these studies. Some studies define clinical resolution as no re-occurrence of acute cholecystitis during follow-up, while other studies rely on imaging and symptom resolution to define clinical improvement. Many studies report on initial clinical success without including re-occurring cases.

This study had some limitations. Only three two-arm studies had available comparative data to conduct a meta-analysis thereby providing a relatively low number of subjects for both drainage method groups (146 for EUS-GBD with LAMS, and 217 with PC) that were used for analysis. Due to the lack of randomized controlled trials, and the comparably small number of subjects in the EUS-GB drainage with LAMS group, it was statistically insufficient to provide a concrete analysis therefore only descriptive outcomes were highlighted. Moreover, the majority of studies exhibited high heterogeneity among reported outcomes. A large retrospective study, (Siddiqui et al.), was excluded as these patients overlapped with patients from other studies. Other limitations of this analysis included the generally low quality of included studies as none were randomized controlled trials therefore they were classified as grade C (see Appendix 1 for grading reference. It was difficult to control for differences in the cholecystostomy methods, i.e. EUS-guided gallbladder drainage versus percutaneous drainage.

Despite limitations, this study provides insight in the comparably newer gallbladder drainage techniques, i.e. EUS-GB drainage with LAMs, that might result in lower morbidity and possibly shorter hospital stay in critically ill patients who are unfit for surgical gallbladder
removal. Other strengths of the present study include the collectively large sample size (a grand total of 3,645 patients (442 LAMS, 3,230 PC)) of included studies and different study types, both retrospective reviews and protective trials. This systematic review and meta-analysis is the largest study to date assessing the safety, and efficacy outcomes of the relatively newer method of EUS-guided gallbladder drainage with LAMS compared to the more established method of percutaneous gallbladder drainage in patients suffering from acute cholecystitis who are not candidates for laparoscopic gallbladder removal.

Conclusions

It is important to note that despite the lack of significant difference in the clinical success outcomes, there are relatively large variations in the reported clinical success rates in these studies, likely due to the definitions of complications. Clinical success or lack thereof can also be correlated with the type of acute cholecystitis, i.e. calculous versus acalculous, since acalculous or even gangrenous cholecystitis are complicated cases can be much more clinically challenging to manage that the typical acute calculous cholecystitis. Significantly lower rates of complications after EUS-guided gallbladder drainage using LAMS could provide a benefit to patients looking for alternative drainage methods in addition to possibly reducing their hospital stay.

Further studies are warranted. Ideally a randomized clinical trial would provide sufficient support for safety and efficacy outcomes, as well as long term outcomes for newer drainage methods and devices, namely LAMS, as studies with LAMS are limited (only one study included in this review provides data for SPAXUS™ apart from limited case reports(Cho, Jo, et al.)).
Nevertheless, this study provides an important analysis of the efficacy and safety of EUS-GB drainage with LAMS in comparison to PC for the management of acute cholecystitis.
Figure 1. Percutaneous Cholecystostomy

_Percutaneous Drainage of the Gallbladder._ The patient is placed under conscious sedation. A local anesthetic is administered to the skin. X-ray images are utilized to position the percutaneous tube in the gallbladder via a guidewire and a needle that is used to puncture the gallbladder. An external bag is used to collect the fluid draining from the gallbladder, until the patient shows meaningful signs of clinical improvement of the acute cholecystitis, after which the drain and bag are removed (A. Smith et al.).
The patient is placed under conscious sedation or monitored anesthesia. An endosonographer uses a linear echoendoscope, a guidewire, and a needle (when electrocautery is not part of the delivery system), and then deploys the distal flange of the stent into the gastric or duodenal lumen and the proximal flange is then deployed into the gallbladder lumen (B) (Dollhopf et al.). Fully deployed stent holds the two lumens into apposition (A) (Baron, Grimm and Swanstrom).
Figure 3. Different Stent Types

A. Percutaneous Drainage Catheter: a 10Fr pigtail, plastic catheter that’s typically placed transhepatically to drain the gallbladder. The other, non-pigtail end, is left outside of the body to drain the infection (Cook_Medical).

B. Niti-S™ SPAXUS™ Stent: Lumen Apposing nitinol-wired Metal Stent fully covered in silicone (left). The SPAXUS™ Stent deliver system (right) (Taewoong_Medical).

C. The AXIOS™ Stent: Lumen Apposing Metal Stent, barbell shaped, fully and partially deployed (Boston_Scientific).

D. AXIOS™ Delivery system: The AXIOS™ stent comes in two types of delivery systems: Electrocautery Enhanced Delivery System also referred to as Hot AXIOS™ (pictured) and the original Delivery System referred to as Cold AXIOS™ (Boston_Scientific).
Figure 4. Flow Diagram of Literature Search

Criteria for selection of the studies included in this systematic review based on inclusion and exclusion criteria

- Records identified through database search: N=1012
- Duplicates Removed: N=426
- Records assessed for eligibility: N=586
- Records Excluded: N=545
  - 152 Intervention and/or outcome not assessed
  - 120 Methodological Reviews
  - 85 Single-patients case reports
  - 31 Wrong disease indication
  - 17 Cannot separate out PC v. CC and/or stent data
  - 15 Letters, videos, interviews, surveys
  - 12 Potential overlap with other studies
  - 5 Consensus statements
  - 2 Conference Proceedings
  - 1 Subjects under 18 years of age

Studies Eligible: N=41
Figure 5. Meta-Analysis of the Comparative Studies

Plots from meta-analysis of the three two-arm studies examining outcomes between EUS-GB drainage with LAMS versus PC for treatment of acute cholecystitis. 

Abbreviations: Perc Drain, Percutaneous Drain; LAMS, Lumen Apposing Metal Stent

A. Clinical Success
B. Technical Success

![Technical Success Graph]

C. Complications

![Complications Graph]

D. Mortality
Table 1. Summary of Lumen-Apposing Metal Stent Products

*Summary of Sizes, material, delivery, and for all marketed LAMS. Abbreviations: EUS-BD, EUS biliary duct drainage; EUS-GBD, EUS gallbladder drainage; EUS-GJ, EUS-guided Gastrojejunostomy; TTS, through-the-scope; PFC, Pancreatic Fluid Collection*

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<th>Flange Diameter (mm)</th>
<th>Stent Body Length (mm)</th>
<th>Introducer Diameter (Fr)</th>
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<th>Deployment Mechanism</th>
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Table 2. Comparative studies

A list of the selected studies that directly compare clinical outcomes between percutaneous cholecystostomy and EUS-guided cholecystostomy using LAMS for the management of acute cholecystitis.

Abbreviations: *RM - retrospective multicenter; RS - Retrospective single center; PS – prospective single center, PM - prospective multi center;

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<th>Design</th>
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<th>Clinical Success PC (%)</th>
<th>Technical Success LAMS (%)</th>
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Table 3. Non-Comparative studies.

A list of the selected studies that report on the clinical outcomes of either percutaneous cholecystostomy or EUS-guided cholecystostomy using LAMS for the management of acute cholecystitis.

Abbreviations: NR, not reported; PS, Prospective Single center; PM, Prospective Multi center; RS, Retrospective Single center; RM, Retrospective Multicenter

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<td>-</td>
<td>-</td>
<td>15</td>
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</tr>
<tr>
<td></td>
<td>(Dollhopf et al.)</td>
<td>2017</td>
<td>RM</td>
<td>75</td>
<td>-</td>
<td>71</td>
<td>96%</td>
<td>-</td>
<td>-</td>
<td>2</td>
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<td>7</td>
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<tr>
<td></td>
<td>(Gunay et al.)</td>
<td>2013</td>
<td>RS</td>
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<td>-</td>
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<td></td>
<td>(Hsieh et al.)</td>
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<td>-</td>
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<td>-</td>
<td>5</td>
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<td>-</td>
<td>-</td>
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<td>NR</td>
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<td>2018</td>
<td>RS</td>
<td>-</td>
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<td>-</td>
<td>85</td>
<td>59%</td>
<td>-</td>
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<td>25</td>
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<tr>
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<td>2015</td>
<td>RS</td>
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<td>NR</td>
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36
|   | Study                          | Year | Method | Total | Hyaline | Chondral | Knee | Total | Hyaline | Chondral | Knee | Total | Hyaline | Chondral | Knee | Total | Hyaline | Chondral | Knee | Total | Hyaline | Chondral | Knee | Total | Hyaline | Chondral | Knee | Total | Hyaline | Chondral | Knee | Total | Hyaline | Chondral | Knee | Total | Hyaline | Chondral | Knee | Total | Hyaline | Chondral | Knee | Total | Hyaline | Chondral | Knee | Total | Hyaline | Chondral | Knee | Total | Hyaline | Chondral | Knee | Total | Hyaline | Chondral | Knee | Total | Hyaline | Chondral | Knee | Total | Hyaline | Chondral | Knee | Total | Hyaline | Chondral | Knee | Total | Hyaline | Chondral | Knee | Total | Hyaline | Chondral | Knee | Total | Hyaline | Chondral | Knee | Total | Hyaline | Chondral | Knee | Total | Hyaline | Chondral | Knee | Total | Hyaline | Chondral | Knee | Total | Hyaline | Chondral | Knee | Total | Hyaline | Chondral | Knee | Total | Hyaline | Chondral | Knee | Total | Hyaline | Chondral | Knee | Total | Hyaline | Chondral | Knee | Total | Hyaline | Chondral | Knee | Total | Hyaline | Chondral | Knee | Total | Hyaline | Chondral | Knee | Total | Hyaline | Chondral | Knee | Total | Hyaline | Chondral | Knee | Total | Hyaline | Chondral | Knee | Total | Hyaline | Chondral | Knee | Total | Hyaline | Chondral | Knee | Total | Hyaline | Chondral | Knee | Total | Hyaline | Chondral | Knee | Total | Hyaline | Chondral | Knee | Total | Hyaline | Chondral | Knee | Total | Hyaline | Chondral | Knee | Total | Hyaline | Chondral | Knee | Total | Hyaline | Chondral | Knee | Total | Hyaline | Chondral | Knee | Total | Hyaline | Chondral | Knee | Total | Hyaline | Chondral | Knee | Total | Hyaline | Chondral | Knee | Total | Hyaline | Chondral | Knee | Total | Hyaline | Chondral | Knee | Total | Hyaline | Chondral | Knee | Total | Hyaline | Chondral | Knee | Total | Hyaline | Chondra |
Table 4. Definition of Outcomes Across Studies

*Definitions for each procedural outcome by study for every one of the comparative studies. Similarities in definitions are highlighted.*

*Abbreviations: ND, Not Defined*

<table>
<thead>
<tr>
<th>Study</th>
<th>Technical Success</th>
<th>Clinical Success</th>
<th>Complications</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Irani, Ngamruengphong, et al.)</td>
<td>the ability to place a percutaneous drainage catheter (PT-GBD) or a transmural LAMS (EUS-GBD) into the gallbladder as determined by <em>flow of bile</em> or pus and confirmed radiographically</td>
<td><em>resolution of symptoms,</em> laboratory, and or radiologic abnormalities within 3 days of intervention.</td>
<td>any procedure, drain, or stent-related event occurring during or within 30 days after the procedure</td>
<td>ND</td>
</tr>
<tr>
<td>(A. Y. B. Teoh et al.)</td>
<td>the ability to access and drain the gallbladder by placement of a drainage tube or stent with immediate drainage of bile.</td>
<td><em>improvement in clinical symptoms</em> and decreasing white cell counts within 5 days after the procedure.</td>
<td>biliary tract-related adverse events after the 30-day period</td>
<td>30-day mortality</td>
</tr>
<tr>
<td>(Tyberg et al.)</td>
<td>successful placement of a catheter or stent into the gallbladder.</td>
<td><em>resolution in clinical symptoms</em> after intervention</td>
<td>ND</td>
<td>Death during hospitalization from sepsis</td>
</tr>
</tbody>
</table>
Table 5. Results from Random-Effect Meta-Analysis

Results of meta-analysis from three comparative studies examining outcomes between EUS-GB drainage with LAMS versus PC for treatment of acute cholecystitis.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Model</th>
<th>Odds Ratio</th>
<th>Lower Limit</th>
<th>Upper Limit</th>
<th>Z-value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Success</td>
<td>Random</td>
<td>2.59</td>
<td>0.39</td>
<td>17.42</td>
<td>0.98</td>
<td>0.3264</td>
</tr>
<tr>
<td>Complications</td>
<td>Random</td>
<td>3.44</td>
<td>1.70</td>
<td>6.98</td>
<td>3.42</td>
<td>0.0006</td>
</tr>
<tr>
<td>Mortality</td>
<td>Random</td>
<td>1.13</td>
<td>0.16</td>
<td>8.18</td>
<td>0.12</td>
<td>0.9063</td>
</tr>
<tr>
<td>Technical Success</td>
<td>Random</td>
<td>4.69</td>
<td>0.91</td>
<td>24.12</td>
<td>1.85</td>
<td>0.0645</td>
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</table>
Appendix 1.

Guidelines’ Grading of Recommendations and Levels of Evidence (Care)

<table>
<thead>
<tr>
<th>Guideline, society or institute, year</th>
<th>Grading of recommendations</th>
<th>Level of evidence</th>
</tr>
</thead>
</table>
| New Grades from Recommendations from the Canadian Task Force on Preventative Health Care, 2003 | A. There is good evidence to recommend the clinical preventive action  
B. There is fair evidence to recommend the clinical preventive action  
C. The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making  
D. There is fair evidence to recommend against the clinical preventive action  
E. There is good evidence to recommend against the clinical preventive action  
L. There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making | I: Evidence obtained from at least one properly randomized controlled trial  
II-1: Evidence from well-designed controlled trials without randomization  
II-1: Evidence from well-designed controlled trials without randomization  
II-2: Evidence from well–designed cohort (prospective or retrospective) or case-control studies, preferably from more than one center or research group  
II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments could also be included in this category  
III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees |
Appendix 2.

MINORS Criteria and Scoring System (Slim et al.)

Methodological items for non-randomized studies

The items are scored 0 (not reported), 1 (reported but inadequate) or 2 (reported and adequate). The global ideal score being 16 for non-comparative studies and 24 for comparative studies.

1. **A clearly stated aim:** the question addressed should be precise and relevant in the light of available literature

2. **Inclusion of consecutive patients:** all patients potentially fit for inclusion (satisfying the criteria for inclusion) have been included in the study during the study period (no exclusion or details about the reasons for exclusion)

3. **Prospective collection of data:** data were collected according to a protocol established before the beginning of the study

4. **Endpoints appropriate to the aim of the study:** unambiguous explanation of the criteria used to evaluate the main outcome which should be in accordance with the question addressed by the study. Also, the endpoints should be assessed on an intention-to-treat basis.

5. **Unbiased assessment of the study endpoint:** blind evaluation of objective endpoints and double-blind evaluation of subjective endpoints. Otherwise the reasons for not blinding should be stated

6. **Follow-up period appropriate to the aim of the study:** the follow-up should be sufficiently long to allow the assessment of the main endpoint and possible adverse events

7. **Loss to follow up less than 5%:** all patients should be included in the follow up. Otherwise, the proportion lost to follow up should not exceed the proportion experiencing the major endpoint

8. **Prospective calculation of the study size:** information of the size of detectable difference of interest with a calculation of 95% confidence interval, according to the expected incidence of the outcome event, and information about the level for statistical significance and estimates of power when comparing the outcomes

*Additional criteria in the case of comparative study*

9. **An adequate control group:** having a gold standard diagnostic test or therapeutic intervention recognized as the optimal intervention according to the available published data
10. **Contemporary groups**: control and studied group should be managed during the same time period (no historical comparison)

11. **Baseline equivalence of groups**: the groups should be similar regarding the criteria other than the studied endpoints. Absence of confounding factors that could bias the interpretation of the results

12. **Adequate statistical analyses**: whether the statistics were in accordance with the type of study with calculation of confidence intervals or relative risk
Appendix 3.

American Society of Anesthesiologist Classification (ASA Class)(Doyle and Garmon)

The latest version of the American Society of Anesthesiologists (ASA) physical status classification system (ASAPS) as approved by the ASA House of Delegates on October 15, 2014 and adapted for this presentation. Note that there is no specific classification assigned to patients with a moderate systemic disease, just assignments for patients with mild systemic disease (ASA 2) and those with severe systemic disease (ASA 3).


- **ASA 1**: A normal healthy patient. Example: Fit, nonobese (BMI under 30), a nonsmoking patient with good exercise tolerance.
- **ASA 2**: A patient with a mild systemic disease. Example: Patient with no functional limitations and a well-controlled disease (e.g., treated hypertension, obesity with BMI under 35, frequent social drinker or is a cigarette smoker).
- **ASA 3**: A patient with a severe systemic disease that is not life-threatening. Example: Patient with some functional limitation as a result of disease (e.g., poorly treated hypertension or diabetes, morbid obesity, chronic renal failure, a bronchospastic disease with intermittent exacerbation, stable angina, implanted pacemaker).
- **ASA 4**: A patient with a severe systemic disease that is a constant threat to life. Example: Patient with functional limitation from severe, life-threatening disease (e.g., unstable angina, poorly controlled COPD, symptomatic CHF, recent (less than three months ago) myocardial infarction or stroke.
- **ASA 5**: A moribund patient who is not expected to survive without the operation. The patient is not expected to survive beyond the next 24 hours without surgery. Examples: ruptured abdominal aortic aneurysm, massive trauma, and extensive intracranial hemorrhage with mass effect.
- **ASA 6**: A brain-dead patient whose organs are being removed with the intention of transplanting them into another patient.

The addition of “E” to the ASAPS (e.g., ASA 2E) denotes an emergency surgical procedure. The ASA defines an emergency as existing “when the delay in treatment of the patient would lead to a significant increase in the threat to life or body part.”
Appendix 4.
Tokyo Guidelines 2018 for Acute Cholecystitis (Yokoe et al.)

**Grade I** (mild) acute cholecystitis

“Grade I” acute cholecystitis does not meet the criteria of “Grade III” or “Grade II” acute cholecystitis. It can also be defined as acute cholecystitis in a healthy patient with no organ dysfunction and mild inflammatory changes in the gallbladder, making cholecystectomy a safe and low-risk operative procedure.

**Grade II** (moderate) acute cholecystitis

“Grade II” acute cholecystitis is associated with any one of the following conditions:

1. Elevated WBC count (>18,000/mm³)
2. Palpable tender mass in the right upper abdominal quadrant
3. Duration of complaints >72 h
4. Marked local inflammation (gangrenous cholecystitis, pericholecystic abscess, hepatic abscess, biliary peritonitis, emphysematous cholecystitis)

**Grade III** (severe) acute cholecystitis

“Grade III” acute cholecystitis is associated with dysfunction of any one of the following organs/systems:

1. Cardiovascular dysfunction: hypotension requiring treatment with dopamine ≥5 µg/kg per min, or any dose of norepinephrine
2. Neurological dysfunction: decreased level of consciousness
3. Respiratory dysfunction: PaO₂/FiO₂ ratio <300
4. Renal dysfunction: oliguria, creatinine >2.0 mg/dl
5. Hepatic dysfunction: PT-INR >1.5
6. Hematological dysfunction: platelet count <100,000/mm³
Appendix 5.
Definition of Terms

AE: Adverse Event

Acalculous Cholecystitis: cholecystitis arising from a cause other than gallstones or cystic duct obstruction

ASA Score: American Society of Anesthesiologists (ASA) score is a global score that assesses the physical status of patients before surgery (Daabiss) (see below)
ASA 1 A normal healthy patient
ASA 2 A patient with mild systemic disease
ASA 3 A patient with severe systemic disease
ASA 4 A patient with severe systemic disease that is a constant threat to life
ASA 5 A moribund patient who is not expected to survive

Calculous Cholecystitis: Cholecystitis with the presence of stones in the gallbladder

CE Mark: CE (European Conformity) Marking is a certification mark that indicates conformity with health, safety, and environmental protection standards for products sold within the European Economic Area. It is the equivalent of FDA approval in Europe.

Cholecystectomy: Surgical removal of the gallbladder

Cholecystitis: Inflammation of the gallbladder

Cholecystolithiasis: Presence of one or more gallstones in the gallbladder

Cholecystostomy: Drainage of the gallbladder

CT scan: computerized tomography is a specialized X-ray scan that produces cross-sectional images of the body using X-rays and a computer
Emphysematous (a.k.a Clostridial) Cholecystitis:

Endoscopic: a non-surgical procedure using an endoscope to visualize the digestive tract

French (Fr): The French size is a measure of the outer diameter of a catheter. The larger the number corresponds to a larger the diameter; abbreviated as Fr.

Gallbladder Empyema: presence of pus in the gallbladder

Gangrenous Cholecystitis: A serious complication acute cholecystitis that arises from increased tension in the gallbladder wall due to acute distention of the gallbladder. The tension leads to tissue death of the gallbladder wall that also may or may not present with cystic artery thrombosis (Chaudhry et al.).

Laparoscopic Cholecystectomy: Minimally invasive, surgical removal of the gallbladder

Lithotripsy: ultrasound shock waves used to break up stones such as gallbladder or kidney stones.

Lumen: cavity within a hollow organ

Systematic Review: A detailed and comprehensive approach of systematically pooling data from multiple selected studies derived a priori with the goal of reducing bias by identifying, appraising, and synthesizing all relevant studies on a particular topic (Uman).

Nasocystic Catheter: Catheter that is inserted through the nasal cavity and into the target organ or cyst.

Nitinol: a metal alloy of nickel and titanium

Percutaneous: through the skin

Percutaneous Transhepatic Cholecystostomy: image-guided placement of drainage catheter into gallbladder lumen passing through or performed by way of the bile
ducts

*Pseudocyst:* refers to pancreatic pseudocyst which is a circumscribed collection of fluid in the pancreas

*Randomized Controlled Trial (RCT):* a clinical study in which subjects are divided randomly in separate groups to be evaluated on two or more different treatments or interventions; the subjects are divided randomly into these groups (Moher, Schulz and Altman)

*Transgastric:* passing through the stomach or duodenum

*Transhepatic:* passing through or performed by way of the bile ducts

*Transluminal:* passing through the lumen of an organ

*Transmural:* existing or occurring across the entire wall of an organ

*Ultrasound:* diagnostic imagining based on the application of ultrasound

*Ultrasonographic:* see ultrasound

*Walled-off Necrosis:* refers to walled-off pancreatic necrosis which is a complication of acute pancreatitis (inflammation of the pancreas) in whereby a collection of fluid and necrotic material begin accruing in the pancreas.

*Xanthogranulomatous Cholecystitis:* a rare form of cholecystitis that presents with a damaging inflammatory response including fibrous tissue, and chronic inflammatory cells. It is often mistaken with malignant gallbladder disease, although the condition is benign (Parra et al.).
Appendix 6.

Abbreviations

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
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<td>AAC</td>
<td>Acute Acalculous Cholecystitis</td>
</tr>
<tr>
<td>ACC</td>
<td>Acute Calculous Cholecystitis</td>
</tr>
<tr>
<td>AKA</td>
<td>Also Known As</td>
</tr>
<tr>
<td>ASA</td>
<td>American Society of Anesthesiologist</td>
</tr>
<tr>
<td>CC</td>
<td>Cholecystectomy</td>
</tr>
<tr>
<td>CT</td>
<td>Computerized Tomography</td>
</tr>
<tr>
<td>ERCP</td>
<td>Endoscopic Retrograde Cholangiopancreatography</td>
</tr>
<tr>
<td>EUS</td>
<td>Endoscopic Ultrasound</td>
</tr>
<tr>
<td>EUS-GBD</td>
<td>Endoscopic Ultrasound Gallbladder Drainage</td>
</tr>
<tr>
<td>EUS-GJ</td>
<td>Endoscopic Ultrasound Gastrojejunostomy</td>
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<td>EUS-BD</td>
<td>Endoscopic Ultrasound Biliary Duct Drainage</td>
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<td>FDA</td>
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<tr>
<td>GB</td>
<td>Gallbladder</td>
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<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
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<tr>
<td>GI</td>
<td>Gastrointestinal</td>
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<tr>
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<td>Intensive Care Unit</td>
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<tr>
<td>LAF</td>
<td>Lumen Apposition Force</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
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<td>--------------</td>
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<tr>
<td>LAMS</td>
<td>Lumen-Apposing Metal Stents</td>
</tr>
<tr>
<td>MINORS</td>
<td>Methodological Index for Non-Randomized Studies</td>
</tr>
<tr>
<td>ND</td>
<td>Not Defined</td>
</tr>
<tr>
<td>PC</td>
<td>Percutaneous Cholecystostomy</td>
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<td>PC-GBD</td>
<td>Percutaneous Gallbladder Drainage</td>
</tr>
<tr>
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<td>Pancreatic Fluid Collection</td>
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<td>Prospective Single center</td>
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<td>Retrospective Multi center</td>
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</tr>
<tr>
<td>TTS</td>
<td>Through the Scope</td>
</tr>
<tr>
<td>WBC</td>
<td>White Blood Cell</td>
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