

Form "EAST Multicenter Study Proposal"

Details #26 (submitted 10/02/2023)

Please indicate if this is a...

New MCT proposal submission

If a revised proposal summarize the changes made to this proposal based on the feedback received:

Study Title

Defining Outcomes of Early vs. Delayed Cholecystectomy for Perforated Cholecystitis

Primary Investigator:

Renqing Wu, MD

Institution that will be the primary site for the study:

University of Texas Southwestern Medical Center, Dallas, TX

Email of Primary Investigator:

renqing.wu@utsouthwestern.edu

Co-PI/second point of contact for the study:

Vanessa Nomellini, MD, PhD

Email of Co-PI/second point of contact for the study:

vanessa.nomellini@utsouthwestern.edu

Are you a current member of EAST?

Yes

If you selected "No" above please identify a Sponsor that is an active EAST member:

Use this area to briefly outline the burden of the problem to be examined.

Gallbladder disease affects approximately 20 million people in the United States, with an incidence of more than 200,000 cases of acute cholecystitis per year. Of those who are estimated to have cholelithiasis, approximately 20% will eventually develop gallstone-related complications, while 80% remain asymptomatic [1]. In acute cholecystitis, the progression of inflammation may lead to ischemia and necrosis, resulting in gallbladder perforation in 2-11% of patients [2]. Male gender, advanced age, presence of cardiovascular comorbidities, and Hispanic ethnicity are all risk factors for the development of gallbladder perforation [3]. The mortality associated with gallbladder perforation is estimated to be 12-42% [4]. While the data on acute cholecystitis would suggest that early operative intervention is associated with improved outcomes, there is a paucity of data to guide the challenges in the management of perforated cholecystitis. Given that gallbladder perforation is the most severe complication of cholecystitis, it is critical to understand the optimal timing for a definitive operation.

Briefly review what major published studies exist on the topic of the proposed project.

The current guidelines recommend early cholecystectomy for acute cholecystitis based on findings from multiple randomized control trials, observational studies, and systematic reviews [5-8]. However, there is lack of evidence to suggest whether early or delayed cholecystectomy is superior to the other in the treatment of perforated cholecystitis [7]. A recent systematic review found no difference in complications and need for further interventions between groups that underwent early versus delayed cholecystectomy; but the study examined a population of 131 patients over 20 years without clearly defining the parameters for early or delayed [9]. In a retrospective single center study, Stefanidis et al found that, in patients with gallbladder perforations, early cholecystectomy within 24 hours of admission resulted in significantly fewer complications and shorter hospital stays. However, this study had a sample size of 30, with laparoscopic cholecystectomy attempted in only eight patients, and successful only in two [3]. Utilizing the NSQIP database, Krecko et al compared outcomes between those who underwent index versus interval cholecystectomy for the diagnosis of gallbladder perforation. They found that those who underwent cholecystectomy during their index hospitalization had longer post-operative hospital length of stay and higher 30-day major morbidity and mortality. However, they were only able to infer about an interval operation, as this data point is not included in the NSQIP database. Furthermore, the study did not stratify patients who underwent laparoscopic versus open cholecystectomy, nor did it specify whether the patients who underwent interval cholecystectomy received a cholecystostomy tube prior [10].

Use this area to briefly outline how this idea is innovative and it's anticipated impact.

Preliminary data from our retrospective analysis of the NSQIP database from 2012-2021 (unpublished) shows that, of the 268 patients with the diagnosis of gallbladder perforation who underwent emergent or urgent laparoscopic cholecystectomy, 99 patients presented with sepsis on admission and the remainder did not. In both groups, early cholecystectomy is associated with shorter length of hospital stay, and decreased risk of intra-operative and post-operative bleeding requiring transfusion, suggesting that it may be beneficial to offer patients with perforated cholecystitis an early, definitive operation. However, we were unable to examine the use of cholecystostomy tube, number of subtotal cholecystectomies, conversion to open cholecystectomy, and additional procedures such as ERCP and percutaneous drain placement, due to the lack of such data points in the NSQIP database. Given the above limitations, the optimal timing for a definitive operation for patients with perforated cholecystitis remains unclear. Our proposed study is innovative in that we will address the limitations in the current literature and existing data to establish evidence based practice on the timing of operation in patients with perforated cholecystitis.

Describe what & how the proposed MCT will add to the existing body of knowledge & literature.

Due to the low incidence of perforated cholecystitis, the data on its management remain sparse, and consist of mostly case studies, case series and single centered studies. Retrospective studies based on large databases, such as NSQIP, fail to capture a comprehensive set of pertinent data points, and often require biased assumptions. A multicentered trial will allow for a more complete collection of pertinent data points, as well as a larger sample size for examining a relatively rare disease, in order to answer to the question of timing of operation for patients with perforated cholecystitis.

Primary aim

To compare the major perioperative complications, rates of re-admission, conversion to open cholecystectomy, re-operation, and need for additional procedures in patients who undergo early (= 48 hours from admission to operation) cholecystectomy for perforated cholecystitis to those who undergo delayed cholecystectomy during the index hospitalization (>48 hours from admission to operation), and to those who undergo cholecystostomy tube placement with interval cholecystectomy during a later admission.

Secondary aims

To identify the most common operative techniques for gallbladder perforation including, but not limited to, laparoscopic cholecystectomy, laparoscopic fenestrated or reconstituted subtotal cholecystectomy, open cholecystectomy, laparoscopic abdominal washout with drain placement, and laparoscopic cholecystostomy tube placement.

Tertiary aim

Design

Retrospective

Inclusion Criteria	Patients with a diagnosis of gallbladder perforation between 01/01/2018-12/31/2023
Exclusion Criteria	Patient < 18 years of age, pregnant patients, patients with traumatic or iatrogenic gallbladder perforations
Please describe, completely but succinctly, how the project will be conducted.	<p>This study will be a multicenter, retrospective review of all patients diagnosed with gallbladder perforation between 01/01/2018-12/31/2023. Each participating center is responsible for obtaining individual IRB approval to access electronic medical record for each patient who meets the inclusion criteria. A data collection tool will be provided, and each center will upload de-identified data to a centralized REDCap database supported by University of Texas Southwestern Medical Center. Data use agreements (DUA) will be obtained should a participating institution require a DUA to share de-identified information. Data will then be collated for analysis.</p>
Primary Outcome	<p>Patients meeting the inclusion criteria will be identified from the ICD 10 diagnosis code of K82.2 within the electronic medical record. The study cohorts will consist of patients who underwent early cholecystectomy, defined as time of admission to time of operation = 48hrs; delayed cholecystectomy, defined as time of admission to time of operation > 48hr but during the same admission; and patients who underwent either antibiotics alone or cholecystostomy tube placement with cholecystectomy during a later admission. The exclusion criteria listed above will be applied, and potential confounding variables will be considered during the statistical analysis.</p>
Secondary Outcome(s)	<p>30 day complication rate based on Clavian-Dindo grade</p> <p>30 day rate of re-admission, ED visits, conversion to open cholecystectomy, subtotal cholecystectomy, total length of stay during initial hospitalization, rate of re-operation, timing of interval cholecystectomy, rate for additional procedures including, but not limited to percutaneous drain placement and ERCP.</p>
Select the variables to be collected & analyzed:	<p>Baseline Participating Institution Information, Demographics, Baseline Clinical Characteristics, Hospital Course, Treatments & Interventions, Outcomes of Interest, Additional variables noted below:</p>

Age, gender, BMI, date of admission, date of operation, number of days from hospitalization to operation, number of days from operation to discharge, hospital length of stay, mortality (date of death), functional status (independent, partially dependent, totally dependent), ASA class, pre-operative steroid use, SIRS, sepsis, or septic shock within 48 hours prior to surgery, co-morbidities including history of ascites within 30 days prior to surgery, ventilator dependence, disseminated cancer, diabetes mellitus with or without insulin, hypertension requiring medication, congestive heart failure 30 days prior to surgery, dyspnea with moderate exertion or at rest, current smoker within 1 year, severe chronic obstructive pulmonary disease, dialysis, acute renal failure, liver disease, presence of US or CT diagnosis of gallbladder perforation, all procedures performed intra-operatively, presence of free perforation, contained perforation or fistula, operative time, return to OR, number of days prior to return to OR, all procedures performed during re-operation, post-operative ERCP, post-operative percutaneous drain placement, superficial wound infection, deep wound infection, organ space wound infection, wound dehiscence, pneumonia, re-intubation, fail to wean from the ventilator for > 48hrs, pulmonary embolism, deep vein thrombosis, acute renal failure, urinary tract infection, cerebral vascular accident, cardiac arrest, myocardial infarction, bleeding requiring intra-operative and/or post-operative transfusion, sepsis, SIRS, or septic shock post-operatively, post operative ICU admission, death, immediate pre-operative Hgb/WBC/Platelet/INR/PTT/Tbili/albumin/Na/lactate/Cr/BUN, ED visits within 30 days post-op or post-cholecystostomy tube placement, re-admissions within 30 days post-op or post-cholecystostomy tube placement, date of interval cholecystectomy and all other of additional interval procedures for patients who underwent initial cholecystostomy tube placement.

Additional variables:

Participating institutions will query their electronic medical record to identify all patients with the ICD 10 diagnosis of K82.2, gallbladder perforation. Each patient's medical record number will then be used to access their record. Data collection will be performed with the tool provided. Each participating institution will then upload each patient's data onto a REDCap database once a DUA has been obtained, should one be required. Each patient will be de-identified and will be given a unique ID number within the study. The REDCap database will be password protected; access will only be given to key personnel participating in the research project at each institution. Once the REDCap database is complete, the PI and Co-PI at the host institution will download and collate the data on password protected computers. Data sharing will only take place between approved research team members through HIPPA compliant emails.

Outline the data collection plan/tool succinctly

Has IRB approval been obtained at the primary site?

No

Is DUA required for participation in the study?

No

If applicable, list the primary contact (name/email) to contact to initiate & execute DUA:

renqing.wu@utsouthwestern.edu

Identify the individuals that will primarily be responsible for data collection process:

The primary investigator will be responsible for data collection at the primary site. Surgical critical care fellows, general surgery research fellows, general surgery residents, medical students, and postdoctoral research fellows will assist in the data collection process.

**Is there a primary
statistician assigned to
assist the PI w/design &
data analysis?**

Yes

**If no, how was study
design/power analysis
determined/who will
handle analysis once
complete?**

**Include detailed
description of the data
analysis plan:**

The Calvian-Dindo Classification will be calculated based on the variables collected, and used to rank the severity of the 30-day post-operative morbidities. Continuous variables will be compared using Student's t-test if it has a normal distribution and Mann Whitney U test if it does not. Categorical variables will be analyzed using chi-squared tests. Skewed data will be reported using median. Categorical variables will be reported as frequencies. Potential confounding variables will be adjusted for and controlled for using multivariate regression model. Statistical significance will be set at $p < 0.05$. All analysis will be two-tailed.

Include Power Analysis:

Based on our preliminary data on 30-day postoperative morbidities from NSQIP, the rate of intraoperative/postoperative bleeding requiring transfusion was 3.85% in those who underwent early cholecystectomy, compared to 13.39% in those who underwent delayed cholecystectomy. Our proposed study will require a total sample size of 270 to achieve an alpha of 0.05 and 80% power.

**Please note what your
enrollment procedure for
this study entails:**

Patients with a diagnosis of gallbladder perforation will be identified at each institution based on query of the electronic medical record. Exclusion criteria will be applied. De-identified data will then be entered into a REDCap database from the medical record. As this is a retrospective chart review with de-identified patient information, no informed consent will be required. Patients will not be paid to participate, nor will there be any cost to the institution or patient as being a part of this study.

**Outline consent
procedures here, if
applicable:**

A waiver of consent is requested, as this will be a retrospective chart review with minimum risk to the participants.

**Please indicate what
resources are available
at the primary study
institution:**

Presence of a dedicated statistician, Research personnel, Availability of data collectors

Include a brief listing of key references:

1. Gallaher JR, Charles A. Acute Cholecystitis: A Review. *Jama*. 2022;327(10):965-75.
2. Derici H, Kara C, Bozdog AD, Nazli O, Tansug T, Akca E. Diagnosis and treatment of gallbladder perforation. *World J Gastroenterol*. 2006;12(48):7832-6.
3. Stefanidis D, Sirinek KR, Bingener J. Gallbladder perforation: risk factors and outcome. *J Surg Res*. 2006;131(2):204-8.
4. Date RS, Thrumurthy SG, Whiteside S, Umer MA, Pursnani KG, Ward JB, Mughal MM. Gallbladder perforation: case series and systematic review. *Int J Surg*. 2012;10(2):63-8.
5. Altieri MS, Brunt LM, Yang J, Zhu C, Talamini MA, Pryor AD. Early cholecystectomy (<?72 h) is associated with lower rate of complications and bile duct injury: a study of 109,862 cholecystectomies in the state of New York. *Surgical Endoscopy*. 2020;34(7):3051-6.
6. Polo M, Duclos A, Polazzi S, Payet C, Lifante JC, Cotte E, et al. Acute Cholecystitis—Optimal Timing for Early Cholecystectomy: a French Nationwide Study. *Journal of Gastrointestinal Surgery*. 2015;19(11):2003-10.
7. Gutt CN, Encke J, Königer J, Harnoss J-C, Weigand K, Kipfmüller K, et al. Acute Cholecystitis: Early Versus Delayed Cholecystectomy, A Multicenter Randomized Trial (ACDC Study, NCT00447304). *Annals of Surgery*. 2013;258(3):385-93.
8. Blohm M, Österberg J, Sandblom G, Lundell L, Hedberg M, Enochsson L. The Sooner, the Better? The Importance of Optimal Timing of Cholecystectomy in Acute Cholecystitis: Data from the National Swedish Registry for Gallstone Surgery, GallRiks. *Journal of Gastrointestinal Surgery*. 2017;21(1):33-40.
9. Quiroga-Garza A, Alvarez-Villalobos NA, Angeles-Mar HJ, Garcia-Campa M, Muñoz-Leija MA, Salinas-Alvarez Y, et al. Localized gallbladder perforation: a systematic review of treatment and prognosis. *HPB (Oxford)*. 2021;23(11):1639-46.
10. Krecko LK, Hoyos Gomez T, Scarborough JE, Jung HS. Postoperative Outcomes after Index vs Interval Cholecystectomy for Perforated Cholecystitis. *J Am Coll Surg*. 2021;232(4):344-9.