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Pilot Study: Operative vs Non-Operative Management of Uncomplicated Acute Appendicitis and Acute Cholecystitis in COVID-19 Positive Patients

PI: Clayton Petro, MD

INTRODUCTION

As the novel coronavirus disease 2019 (COVID-19) disseminates across the United States, more routine preoperative testing is going to expose the 81% of infected patients with no or mild pneumonia symptoms.(1) Surgeons are going to face challenging decisions regarding whether or not to operate for non-elective cases requiring general anesthesia when non-operative treatment options exist.

Currently, little is known regarding the true consequences of general anesthesia in COVID-positive (COVID+) patients. A series of 34 COVID+ patients from Wuhan who underwent elective surgery found that all patients developed postoperative pneumonia with abnormal findings on CT, 15 (44%) required a postoperative ICU-admission, and 7 (21%) died. That said, "low-risk" surgical procedures – as defined by the National Health Commission of China – carried a low ICU-admission rate (1/12, 8%) and no mortalities. (2) Another series of 3 patients from Iran who underwent elective operations describes concerning postoperative pulmonary complications culminating in 2 (66%) deaths.(3) While the decision to delay elective surgery is practical in COVID+ patients, those presenting with urgent operative indications can present more difficult scenarios.

Specifically, COVID+ patients with uncomplicated acute appendicitis could be treated non-operatively with antibiotics.(4) Likewise, COVID+ patients with acute cholecystitis could be treated with antibiotics or a percutaneous cholecystostomy tube.(5, 6) Either approach could obviate or delay the need for an operation with general anesthesia until the patient has recovered from their viral illness. However, patients managed without a definitive operation may alternatively result in more resource utilization, PPE consumption, interactions with hospital personnel, and treatment failures that could exacerbate their concomitant viral illness. Therefore, we hypothesize that COVID+ patients with uncomplicated acute appendicitis or acute cholecystitis amendable to a laparoscopic procedure can have safe operative outcomes compared to those managed non-operatively. Given the paucity of literature on this topic, we will enroll patients in a pilot study and monitor for safety primarily as defined by: a) pulmonary complications. Secondary outcomes will include b) post-intervention ICU admission, c) mortality, d) overall complications measured by the Clavien-Dindo classification and comprehensive complication index, e) hospital length of stay, f) emergency room visits/readmission, and g) failure rates of non-operative management.

STUDY DESIGN

This will be a prospective, non-blinded, pilot randomized controlled trial with a 1:1 allocation ratio. No important changes to the methods are anticipated. This will be a multi-center study coordinated at the Main Campus of Cleveland Clinic Foundation (CCF) in Cleveland, Ohio with enrollments performed at Main Campus, Fairview, Hillcrest, Marymount, Lutheran, South Pointe, and Akron General Hospitals. Data will be collected in a secure CCF REDCap. Investigator training will occur through one or more virtual meetings in which the study PI will

review procedures for screening and randomization, inclusion and exclusion criteria, and details of management of both study arms with each enrolling surgeon. Enrolling surgeons will be provided slides containing this information for reference as well.

Specific inclusion criteria are:

- ≥18 years old
- COVID-19 confirmed positive by a microbiologic test within 14 days of a COVID diagnosis
- Mild COVID-19 – no or mild pneumonia ultimately. Diagnosis at the discretion of the attending surgeon (*see exclusion criteria)*.(1)
- EITHER
    - Uncomplicated acute appendicitis ~~without a fecalith~~

      OR

    - Acute cholecystitis – by TG18/TG13 diagnostic criteria(7)
        - A. Local signs of inflammation etc.
            - (1) Murphy's sign, (2) RUQ mass/pain/tenderness
        - B. Systemic signs of inflammation etc.
            - (1) Fever, (2) elevated CRP, (3) elevated WBC count
        - C. Imaging findings
            - Imaging findings characteristic of acute cholecystitis
        - Definite diagnosis: one item in A + one item in B + C

Specific exclusion criteria are:

- Active pregnancy
- Positive COVID test more than 14 days prior to surgical consultation.
- COVID-19 severe disease that would be a contraindication to operative intervention at the discretion of the attending surgeon supported by the following, none of which are individually required or are a strict exclusion criterion as some of these could be attributed or exacerbated by the underlying surgical problem:
    - Persistent dyspnea
    - Persistent respiratory frequency ≥30/min
    - Persistent blood oxygen saturation ≤93%
    - Partial pressure of arterial oxygen to fraction of inspired oxygen ratio <300
    - Lung infiltrates >50%
- COVID-19 critical disease – respiratory failure, shock, or multiorgan dysfunction
- The surgeon expects increased operative complexity – high risk of conversion to open or prolonged procedure
- Unable or unwilling to consent or fulfill study procedures – need to complete 90 day follow-up by telephone

The study will consist of two treatment arms, assigned in a 1:1 fashion. (1) Non-operative management, and (2) operative management.

1. Non-operative management – Patients will be treated with 2-3 days of intravenous antibiotics followed by 7 days of oral antibiotics, as described below:

   Non-penicillin allergic patients –

   - piperacillin/tazobactam 3.375g IV every 6 hours for 2-3 days
   - amoxicillin/clavulanate 875/125mg by mouth every 12 hours for 7 days

   Penicillin allergic patients –

   - ertapenem 1g IV every 24 hours for 2-3 days
   - ciprofloxacin 500mg every 12 hours AND metronidazole 500mg every 8 hours for 7 days

   Patients may be considered to have failed non-operative management (e.g. treatment failure) if they experience absence of clinical improvement, worsening abdominal pain and/or localized/diffuse peritonitis in the judgment of the treating surgeon at any point within the study window. If this occurs, then surgeons may proceed with rescue appendectomy or percutaneous drainage in the setting of appendicitis, or with placement of a percutaneous cholecystostomy tube in the setting of acute cholecystitis.

2. Operative management – Patients will undergo surgical removal of the affected organ. The initial approach will be in a minimally invasive, laparoscopic fashion. If necessary, conversion to an open operation may be performed, and these patients will be included in analysis in an intent-to-treat fashion. These patients will be treated preoperatively and postoperatively with similar antibiotic regimens, however the duration of IV and PO antibiotic therapies will be dependent on factors such as intraoperative findings, resolution of laboratory abnormalities, and tolerance of PO medications.

A computer-generated randomization scheme will be built by a CCF. Randomization will take place on the Research Electronic Data Capture (REDCap®) database program. Patients will be randomized to operative management or non-operative management immediately after signing consent, within 36 hours of surgical consultation at the treating hospital. They will be informed regarding the management that they will receive. The staff surgeon will document their planned treatment using a standardized dot-phrase.

OUTCOMES TO BE INVESTIGATED

PRIMARY OUTCOME MEASURES

1. Pulmonary complications – Including pneumonia, acute respiratory distress syndrome (ARDS) or unexpected postoperative ventilation. Time Frame: initial hospital admission and within 90 days of randomization.

a. For operative cases – any episode of non-invasive ventilation, invasive ventilation, or extracorporeal membrane oxygenation after initial extubation after surgery, or patient cannot be extubated as planned after surgery.
b. For non-operative cases – any intubation.

SECONDARY OUTCOME MEASURES

2. Post-intervention ICU admission – Time Frame: initial hospital admission and within 90 days of randomization

3. Mortality – Time Frame: initial hospital admission and within 90 days of randomization

4. All complications as measured by the Clavien-Dindo classification – Time Frame: within 90 days of enrollment.

5. Hospital length of stay

6. Emergency room visits/readmission – Time Frame: within 90 days of enrollment.

7. Treatment failure for non-operative management. – Time Frame: initial hospital admission and within 90 days of randomization

Specific Aim #1: To determine if patients with mild COVID-19 and appendicitis or cholecystitis managed operatively have greater rates of pulmonary complications compared to similar patients managed nonoperatively

The primary outcome is pulmonary complications after randomization. These outcomes will be recorded for the initial hospital stay, as well as for the 90-day follow-up period.

Specific Aim #2: To determine if patients with mild COVID-19 and appendicitis or cholecystitis managed operatively have different rates of ICU admission after randomization compared to patients managed non-operatively.

For all cases, this will be considered to be any ICU admission occuring after randomization. ICU admission will be recorded as a categorical outcome, and for patients who are admitted to the ICU, the duration of ICU admission in hours will be recorded as well. These outcomes will be recorded for the initial hospital stay, as well as for the 90-day follow-up period.

Specific Aim #3: To determine if patients with mild COVID-19 and appendicitis or cholecystitis managed operatively have different rates of mortality compared to patients managed non-operatively.

Mortality at the index hospital admission and within 90-day follow-up period will be recorded as a categorical outcome. Date and cause of mortality will also be recorded.

Specific Aim #4: To determine if patients with mild COVID-19 and appendicitis or cholecystitis managed operatively have greater rates and/or severity of complications, as measured by Clavien-Dindo scale, compared to patients managed non-operatively.

Complications after randomization will be recorded prospectively using Clavien-Dindo scale and Comprehensive Complication Index. Rates and severity of complications will be compared between groups.

Specific Aim #5: To determine if patients with mild COVID-19 and appendicitis or cholecystitis managed operatively have shorter length of hospital stay compared to patients managed non-operatively.

Length of stay will be recorded from time of randomization to time of index hospital discharge. Additionally, length of any hospital readmissions will also be recorded.

Specific Aim #6: To determine if patients with mild COVID-19 and appendicitis or cholecystitis managed operatively have decreased rates of hospital readmission or ED visits in the 90 days after initial randomization compared to patients managed non-operatively.

Patients will be contacted at 90 days after hospital discharge and will be asked whether they have had any additional visits to the ED or hospital readmissions. If patients are unable to be reached, available data within the electronic medical record will be used. If available, number of ED visits/readmissions and length of hospital readmissions will also be recorded.

Specific Aim #7: To determine the rate and timing of failure of nonoperative management for patients with mild COVID-19 and appendicitis or cholecystitis managed nonoperatively.

Patients may be considered to have failed non-operative management (e.g. treatment failure) if they experience absence of clinical improvement, worsening abdominal pain and/or localized/diffuse peritonitis. If this occurs, then surgeons may proceed with rescue appendectomy or percutaneous drainage in the setting of appendicitis, or with placement of a percutaneous cholecystostomy tube in the setting of acute cholecystitis. If this occurs, the date of failure of nonoperative management will be recorded, and these patients will remain considered in the group to which they were originally assigned (e.g. intent-to-treat analysis).

ANTICIPATED TIME FRAME

Estimated patient accrual time is six months with data collection to occur over 90 days from the last enrolled patient. Data analysis and manuscript production will occur within one month of completion of data collection.

PATIENT RISKS AND DISCOMFORTS

The effect of mild COVID-19 on outcomes after lower-complexity surgery for non-elective surgical conditions is unknown. Therefore, the major risk associated with the study is that we simply cannot predict what the outcomes are going to be. As detailed later, a Data Safety Monitoring Board will be convened to monitor outcomes routinely to ensure that patients are not being placed at undue risk. Beyond this, both operative and non-operative management strategies

of acute cholecystitis and acute appendicitis are used regularly and both represent relatively low risk.

PATIENT BENEFITS

There are no direct benefits to subjects for participation in this study. Study participation will, however, help physicians and hospital administrators better understand outcomes of patients with mild COVID-19 presenting for management of non-elective surgical conditions.

COSTS TO THE SUBJECTS

There are no extra costs to the subjects associated with this research endeavor. Procedures related to preoperative evaluation, any surgery or intervention, and other hospital and post-hospital care are considered standard of care and will be billed to the subject or the subject's insurance company.

ALTERNATIVES TO PARTICIPATION

Patients are under no obligation to participate in this study. The investigators will discuss all available surgical options with patients. It will be emphasized that refusal to participate in this study will not impact any patient's ability to receive care at participating sites.

PAYMENTS TO SUBJECTS

There will be no direct payments or financial benefit to the subjects. Participation will be voluntary.

PLAN FOR OBTAINING INFORMED CONSENT

For each subject, written informed consent will be obtained prior to any protocol-related activities. As part of the informed consent procedure, the principal investigator, surgeon co-investigator, or one of the approved study coordinators will explain verbally and in writing the nature, duration, and purpose of the study in such a manner that the subject is aware of potential risks, inconveniences, or adverse effects that may occur. Subjects will be informed that they may withdraw from the study at any time and will receive all information required by federal regulations.

Following identification of a potential study participant, the investigator or co-investigator will be responsible for instituting the informed consent process in a face-to-face manner. Before starting any study procedures, the investigator will discuss the proposed research study in detail with the potential subject to discuss treatment options. The subject will be allowed ample time to read and review the informed consent document and to ask questions. The informed consent document will be reviewed with the subject in depth by the participating investigator or by a designated member of the research team to ensure that the potential participant has a thorough understanding of the study protocol and understands the potential risks and benefits of study participation and his or her rights as a study participant. After

consideration, the subject may ask additional questions before signing the informed consent document to participate in this study. Patients may ask for additional time to consider study participation, however the decision to participate should occur within 36 hours of surgical consultation at the presenting hospital so as not to delay treatment for these non-elective conditions.

Patients will be provided with the information sheet on COVID-19 clinical trials at the Cleveland Clinic. If a patient is in quarantine and cannot provide informed consent process in the face-to-face manner described above, the following COVID consent process measures will be taken:

1. A copy of the consent will be provided to the subject by a health care worker who has entered the room.
2. The informed consent will be conducted over the phone by an investigator or research nurse knowledgeable about the research and an uninvolved witness.
3. The consent will be taken to our research office by the health care worker who entered the room and placed in a secure/locked cabinet.
4. Documentation of the consent will be placed in EPIC per IRB policy.
5. If the consent document is not able to be collected, one of two options will be performed:
    a. Attestations by the witness who participated in the call and by the investigator or research nurse that the patient confirmed that they agreed to participate in the study.
    b. A photograph of the informed consent document with attestation by the person entering the photograph in the study record that states how the photograph was obtained and that it is a photograph of the informed consent signed by the patient.

PROVISIONS FOR SUBJECTS FROM VULNERABLE POPULATIONS

The population to be studied includes adults of at least 18 years of age. Children, cognitively-impaired persons, pregnant women, students and house staff under the direct supervision of the investigator are considered vulnerable populations and will, therefore, be excluded from participation. If a staff member or employee of the participating institutions is a potential candidate for the study, the subject will be informed during the consent process that his/her participation or refusal to participate will not influence grades, employment, or subsequent recommendations.

If a subject cannot read a consent form due to illiteracy or blindness, a member of the research study staff will read and explain the consent form to the participant or to the participant's legally-authorized representative. A witness who will sign and date the consent form must be present during this encounter.

SUBJECT PRIVACY AND DATA CONFIDENTIALITY

Subject anonymity and data confidentiality will be maintained throughout this study. Every effort will be made to maintain the confidentiality of documents that identify the subject by name (e.g., signed informed consent documents, clinic charts), except to the extent necessary to allow monitoring by the Offices of Research Compliance at the participating institutions or by other regulatory authorities.

All of the information collected, such as name or medical record number, will be stored in REDCap®, or in an Excel file stored in a secure network folder to which only the investigators at each site have access. Randomization will occur with the use of a customized REDCap® database program housed at CCF, a secure network/firewall-protected electronic database for which only the investigator and the designated members of the study team will have access using an individually-assigned login and password. Only approved study members listed on the IRB protocol will have access to a separately-stored master list. Only the Principal Investigator, Lead Research Coordinators, and Biostatisticians will be granted access to retrieve patient data for data quality assessment and data analysis. All electronic records pertaining to the clinical study will be password-protected and only approved study members listed on the IRB protocol will have password access.

SAMPLE SIZE / POWER CALCULATION

A total of 50 patients are planned to be enrolled in this trial, with approximately 25 patients enrolled in each arm. A power calculation was not performed as the goal of this study is to act as a pilot study to evaluate the safety of both management strategies for patients with mild COVID-19 and to provide surgeons with high-quality, useful data to engage in shared decision-making with patients while future larger studies are pending. Because acute cholecystitis and acute appendicitis have similar expected operative times and postoperative lengths of stay and similar postoperative complication rates, we do not intend to stratify by disease process. Additionally, the primary outcome of pulmonary complications should not be greatly influenced by which presenting disease process a participant has, as it is rare for a patient to remain intubated after either cholecystectomy or appendectomy.

STATISTICAL ANALYSIS

Descriptive statistics, including means, standard deviations, and/or percentages, will be calculated for demographic and baseline variables. Categorical variables will be reported using proportions. Continuous variables will be reported using either means and standard deviations for normally distributed data or median and interquartile range for non-normally distributed data. Appropriate statistical tests including Chi square and/or Fisher's exact tests for comparisons of proportions and t-tests and/or Mann-Whitney U-tests for comparison of continuous variables will be used. R software will be used for all analyses. A two-tailed p-value <0.05 will be considered statistically significant. Analysis will be performed in an intent-to-treat fashion.

DATA SAFETY MONITORING BOARD

As mentioned previously, the major risk associated with the study is that we cannot predict what the outcomes are going to be for these patients as there is little high-quality literature surrounding COVID-19 in surgical contexts. A Data Safety Monitoring Board will be convened to monitor outcomes routinely to ensure that patients are not being placed at undue risk. We will plan to review outcomes after 20 and after 40 patients enrolled in the study.

The progress of the study including safety events will also be reviewed through weekly communication among study investigators. Safety events that will be reviewed will include any instances of intraoperative adverse events, pulmonary complications, ICU admission, and hospital readmission. Collection of this safety information will be ongoing, and review of this information will occur on a weekly basis. Additionally, a monthly phone and/or virtual conference call between site PIs and research coordinators and fellows will be held to address study progress and ensure that there is an opportunity to resolve any outstanding issues.

CLINICAL SIGNIFICANCE/INNOVATION

COVID-19 presents a substantial dilemma to surgeons in the context of non-elective surgical problems. Determining whether proceeding with definitive surgical management of common acute disease processes in the context of mild COVID-19 is safe compared to nonoperative management will be a major step forward in our understanding of how to manage such patients with common surgical conditions in the months and years to come.

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