

ANSWERING REVIEWERS

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Manuscript NO: 70257

Title: Surgical treatment of acute cholecystitis in patients with confirmed COVID-19:
Ten case reports and review of literature

Authors: Katya Bozada-Gutiérrez, Mario Trejo-Avila, Fátima Chávez-Hernández, Sara Parraguirre-Martínez, Carlos Valenzuela-Salazar, Jesús Herrera-Esquivel, Mucio Moreno-Portillo

Dear Editor,

We intend to publish our manuscript entitled: "Surgical treatment of acute cholecystitis in patients with confirmed COVID-19: Ten case reports and review of literature".

The revisions were performed according to the Peer-Review Report (3 reviewers) and according to the revisions suggested by the Science Editor.

We would like to thank the editors and reviewers involved in the revision of our manuscript. All your comments were very welcome by the authors, and appropriate changes were made.

We consider that after these revisions our paper is ready for re-review and for publication.

COMMENTS FOR THE AUTHOR:

Science Editor:

This retrospective cohort study described surgical treatment of acute cholecystitis in patients with COVID-19 disease. As the case number is ten, this study seems to be a cases report instead of an original article. The authors should describe the reconstituting subtotal cholecystectomy, a bailout procedure, in details. For example, which part of the gallbladder (neck, infundibulum or posterior wall on the liver bed) was left in the patient bodies? Was any attempt to close the intraluminal opening of cystic duct? Provision of photos of this bailout procedure is strongly suggested.

RESPONSE:

We described the bailout procedure in details, adding the following paragraph: “. The reconstituting subtotal cholecystectomy consisted in making an incision in the gallbladder, aspirating the contents including the stones, removing the peritonealized portion of the gallbladder, except the lowest portion (infundibulum and Hartmann’s pouch), and partially excising the posterior wall adherent to the liver. After that, the lowest part of the gallbladder is closed with sutures obliterating the cystic duct , leaving a closed gallbladder remnant ^[15, 42]. ”

Unfortunately, we did not have photos of the bailout procedure.

COMMENT:

The “Discussion” section is surprisingly short. Although the authors provide detailed perioperative descriptions of these ten patients, little additional information could be obtained. All the hypotheses of the association of SARS-CoV-2 with cholecystitis came from several previous studies.

RESPONSE:

We added paragraphs to the discussion section. An extensive review of literature concerning acute cholecystitis in patients with confirmed COVID-19 was performed. Table 4 summarized the published manuscripts concerning this topic.

Although this manuscript described the results of only 10 patients, our study represent one of the largest series of cholecystitis in confirmed COVID-19 patients.

Most of the published papers had larger sample sizes but they also included negative SARS CoV 2 patients.

We try to summarize all the published literature concerning this topic in one table. This is why the discussion section is short. However we added more paragraphs to the discussion section of the manuscript as suggested.

COMMENT:

Besides, there is no explanation for the incredible high biliary leak rate ($5/10 = 50\%$) as well as the possible solution. For example, T-tube or transcystic C-tube placement may help to prevent a biliary leak in case of cystic duct necrosis found intraoperatively.

RESPONSE:

In our hospital, all our cystic duct leaks are treated with ERCP (sphincterotomy or stent). We did not employ T or C tubes.

In our series, five patients developed biliary leak after subtotal cholecystectomy. Of these patients, two had low-output leak, while three patients had high-output biliary leak. The 2 patients with low-output leaks resolved with drainage alone, while 3 patients required ERCP

We made the following corrections in the manuscript: "Patients with low-output leaks were treated with closed suction drainage alone, while patients with high-output leaks needed ERCP with biliary sphincterotomy and biliary stent placement."

As mentioned in the 2018 Tokyo Guidelines "More patients whose surgery concluded with drainage because the stump of the neck of the GB was not closed underwent postoperative endoscopic retrograde cholangiography compared with those in whom closure was successfully performed, but there was no change in the rate of complications."

The incidence of biliary leak after subtotal cholecystectomy is high and in a meta-analysis it is reported as high as 18% (Elshaer M, Gravante G, Thomas K, Sorge R, Al-Hamali S, Ebdewi H. Subtotal cholecystectomy for "difficult gallbladders": systematic review and meta-analysis. JAMA Surg. 2015 Feb;150(2):159-68. doi: 10.1001/jamasurg.2014.1219.)

COMMENT:

Besides, the reason of defining open conversions as bailout procedures was unknown. Open conversions should be regarded as successful procedures to save patients rather than failed laparoscopic operations.

RESPONSE:

Considering open conversion as a bailout procedure is based on the Tokyo guidelines as referred in the manuscript.

Tokyo guidelines considered as bailout procedure the following: open conversion, subtotal cholecystectomy, funds first, and cholecystostomy.

“Since the Tokyo Guidelines 2013 (TG13), an attempt has been made to assess intraoperative findings as objective indicators of surgical difficulty; based on expert consensus on these difficulty indicators, bail-out procedures (including conversion to open cholecystectomy) have been indicated for cases in which LC for AC is difficult to perform.”

Reference #42: (**Wakabayashi G**, et al. Tokyo Guidelines 2018: surgical management of acute cholecystitis: safe steps in laparoscopic cholecystectomy for acute cholecystitis (with videos). *J Hepatobiliary Pancreat Sci* 2018; **25**: 73-86 [PMID: 29095575 DOI: 10.1002/jhbp.517])

COMMENT:

Furthermore, the complication grading based on Clavien-Dindo classification was confusing. Antipyretic and analgesic administration is a common practice during the postoperative course and should not be referred to grade I complication.

RESPONSE:

Thank you.

Clavien dindo classification included as grade I any deviation from the normal postoperative course, and the allowed therapeutic regimens for grade I are: antipyretics, analgesics, diuretics, electrolytes and physiotherapy.

To avoid confusion, we corrected and edited Table 3.

COMMENT:

Based on the finding that total episodes of grade IVa were 17, at least two patients suffered from multiorgan failure, but there was only one patient in grade IVb complication.

RESPONSE:

There was a mistake in that Table. The correct number of patients with multi organic failure is five. We corrected that number in Table 3.

COMMENT:

The " Conclusion" section provides little new or constructive information.

RESPONSE:

Thank you, we believe that the novelty of the study is the description of 10 patients with confirmed COVID-19 with complicated cholecystitis. Surgeons operating patients

with COVID-19 should be prepared for a difficult cholecystectomy and to perform a bail out procedure.

We added the following sentence in the conclusion section:

“In conclusion, we found in the present study that patients with confirmed SARS-CoV-2 infections who presented with acute cholecystitis, tended to have a higher grade on the Parkland grading scale (including gallbladder perforation, empyema and total wall necrosis), had difficult laparoscopic cholecystectomies with an increased need for a bail-out procedure, had high rates of ICU admission, and had a prolonged length of hospital stay. As suggested by our case series and previously published literature, we advise to surgeons performing cholecystectomy in confirmed SARS-CoV-2 patients to be prepared for a difficult surgery and to consider a bail-out procedure to prevent secondary damage.”

COMMENT:

The total references number (n=49) is enough. 96% (47/49, higher than 50%) of the cited references represent publications from the recent 5 years.

RESPONSE:

Thank you for the comment. This is a current and evolving topic since the pandemic started last year.

COMMENT:

The units of Age and BMI are missing in Table 1.

RESPONSE:

We added the units of age and BMI in table 1

COMMENT:

Although the authors provide an English editing certificate from American Journal Experts, but the language quality is grade B. Some minor grammar mistakes need to be polished.

RESPONSE:

We checked for grammar mistakes and we obtained a new certificate from the American Journal Editors.

COMMENT:

All authors must provide their personal ORCID registration number. Please visit the ORCID website at <https://orcid.org/> for more information.

RESPONSE:

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COMMENT:

The “Supportive foundations” section is missing. Please provide it after the “Author contributions” section.

RESPONSE:

We did not receive supportive foundations.

We added the following sentence: “No grants or other financial support were received”

Reviewer #1:

Comment:

Reviewer #1:

Greetings, here are some insights regarding the Manuscript:

1. According to the manuscript in full content, in the abstract, the aim should state perioperative assessment and afterward use the word POSTOPERATIVE outcomes rather than “...the *perioperative* outcomes...” in that specific sentence to be precise.

RESPONSE 1:

We appreciated the reviewer’s comments. Here we present point by point response to reviewer comments.

We have changed the aim as suggested: “To describe the perioperative assessment and postoperative outcomes of patients with confirmed SARS-CoV- 2 infection with concomitant acute cholecystitis who underwent cholecystectomy. ”

Comment 2. State why the patients were screened or had SARS-CoV-2 infection within the differential diagnostics, for them to be tested by reverse-transcriptase polymerase chain reaction (RT-PCR) assay of a nasopharyngeal swab or a rapid antigenic test.

RESPONSE 2:

We added to the materials and method section of the manuscript the following sentence: "During the pandemic all the patients that were admitted to our hospital were screened for SARS-CoV-2 infection.."

Comment 3. Multiple grammar corrections such as spelling number of patients with words, punctuation among others, for example, here would be a better way to draft the Results within the abstract:

A total of 10 SARS-CoV-2 positive patients with concomitant acute cholecystitis were analyzed. Six were males, the mean age was 47.1 years, the mean BMI was 28.4, and 6 patients were classified as high risk according to the qSOFA score. Nine patients had moderate, and one patient had severe acute cholecystitis. All patients were treated with urgent/early laparoscopic cholecystectomy. Regarding the Parkland grading scale, two patients were Parkland 3, two were Parkland 4, and six were Parkland 5. Eight patients required a bail-out procedure (6 required subtotal reconstituting cholecystectomy and two open conversions). The mean blood loss was 258 mL, the mean operative time was 133.5 min, and eight patients required closed intraabdominal drainage. Four patients developed a biliary leak after subtotal cholecystectomy and required ERCP with biliary sphincterotomy and biliary stent placement. After surgery, five patients required ICU admission, which developed ARDS related to SARS-CoV-2. One patient died after cholecystectomy due to ARDS complications. Considering the complete cohort, the mean total length of stay was 18.2 days. The histopathological diagnosis demonstrated transmural necrosis (n= 5), hemorrhagic infarction (n= 2), vessel obliteration with ischemia (n= 3), gallbladder wall perforation (n= 3), and acute peritonitis (n= 10).

RESPONSE 3:

As suggested in comment #3, we edited the abstract section concerning grammar corrections.

We also corrected the spelling of the number of patients and checked for punctuation errors.

COMMENT 4. Methods, results, and discussion are thoroughly well structured and have valuable scientific content, with only minor grammar mistakes to be polished.

RESPONSE 4:

Thank you for the comment. Minor grammar mistakes were corrected. A new grammar certificate was received.

Reviewer #2:

Comment: No comments

Response to Reviewer #2: Thank you. No comments from reviewer #2

Reviewer #3: Authors did a fine job reporting their findings. All parts of the paper, introduction, methods, results and especially literature review and discussion is presented in a nice and concise way. Although the findings reported by authors have been extensively reported in the literature previously (which they have also discussed), I would publish this paper only for the literature review. No further remarks.

Response to Reviewer #3: We would like to thank reviewer #3 for the comments.

Thank you,

Mario Trejo-Avila, M.D.

Corresponding author