

Dear Editors,

We wish to re-submit this original article entitled " Which octogenarian patients are at higher risk after cholecystectomy for symptomatic gallstone disease? A single center cohort study." to be considered for publication in the World Journal of Clinical Cases.

We are grateful to you and your reviewers for their valuable suggestions. We have incorporated all changes/ suggestions to the manuscript according to the reviewers' comments. Incorporating those suggestions has enhanced our manuscript significantly. We thank the reviewers for their positive input.

We hope that the reviewers and your team find our article interesting and novel meriting publication. We hope that our response to their comments / criticisms is satisfactory.

In anticipation,

Yours Sincerely,

Leonardo Solaini on behalf of all authors

Reviewer #1:

1. The authors presented a retrospective multivariate and univariate analysis in patients over 80 years of age with cholecystectomy. The treatment strategy for cholelithiasis or acute cholecystitis varied widely among institutions. Although the authors stated that they followed the Tokyo guidelines, relatively larger number of urgent cases and presence of patients with cholangitis or underwent choledochotomy suggest that a bias in the institutional policy that cannot be ignored.

Authors' reply: The treatment of the complications of cholelithiasis is a field extremely challenging and complex. In our center elderly patients with cholangitis have been addressed to antibiotic therapy ± endoscopic/percutaneous biliary drainage since 2004. This is in line with TG18.

This policy also justifies the number of ERCP performed in the preoperative setting in our cohort.

However, it is not always possible to solve the clinical problem with one preoperative procedure and in those cases we chose to perform an intraoperative endoscopic "rendez vous". When this is not sufficient, it could be followed by choledocholithotomy. This is also in line with TG18 where it is stated "If the underlying etiology requires treatment, this should be provided after the patient's general condition has improved;endoscopic sphincterotomy and subsequent choledocholithotomy may be performed together with biliary drainage".

Furthermore, it must be noted that the population aged >80 have a high rate of BII reconstruction for partial gastrectomy performed 40-60 years earlier for benign disease. This limits the utility of endoscopic treatment of choledocholithiasis, leaving choledocholithotomy as the only therapeutic option. In addition, our center is an HPB hub for the region and this allowed more complex cases to be centralized in our institution.

2. In particular, cholecystectomy was not recommended by the guidelines for ASA4 patients.

Authors' reply: As stated in material and methods we used TG18 in order to retrospectively classify the cholecystitis included in the cohort. Treatment flowchart was not strictly followed as these guidelines were published at the very end of the study interval.

Still, all cases at risk were discussed multidisciplinary with endoscopists and anesthesiologists before indicating surgery

Thus, analysis of the data after the large selection bias would not appeal to leaders.

In order to reduce the bias of the institutional criteria, it would be better to perform the comparative analysis with patients under 80 years of age (otherwise 65 to 79 years old).

If the authors would like to focus on patients over 80 years of age, a comparative analysis with patients who did not undergo cholecystectomy but were treated the disease endoscopically or percutaneously would be more informative.

Authors' reply: Authors' reply: As stated above, our study protocol did not include the need to have a control group as the aim of the study was to revise all octogenarians that had cholecystectomy and to find risk factors that could help surgeons in the decision process leading to both emergency and elective surgery in this particular population.

Neither NICE 2018 nor TG18 suggest an age cut-off to surgically treat symptomatic gallstone disease or cholecystitis, based on the literature reporting similar results between elderly and control groups. In addition, TG 18 recommend the most complex cases in those centers with best skills in HPB surgery (as it is our institution).

TG18 recommended the evaluation of perioperative risk according to ASA score and Charlson Comorbidity index. This study tried to explore other variables which could have helped in this assessment.

As stated above, TG18 were published at the end of the study interval and they could not be followed retrospectively. However, the decision of performing cholecystectomy in most complex cases was shared in multidisciplinary discussion.

However, we noted that few statements on the safety of cholecystectomy on octogenarians could not be done without a control group and we corrected them.

4. There was no description about the definition of complicated or uncomplicated in terms of the Clavien-Dindo classification.

We chose not to describe the Clavien-Dindo classification as we assumed they were an well-established definition in surgical literature.

It was confusing whether “grade >2” was the same as “Clavien-Dindo 3 or 4”, otherwise two different meaning.

Authors’ reply: thank you we corrected the text accordingly.

The 90-day mortality rate was 3.9% in the Results section and 2.6% in the Discussion section. Thus, the numbers in the data were not reliable. In the discussion, the authors claimed that the complication rate for grade >2 was low at 9.7%, but they did not provide specific data from the references.

Authors’ reply: The 90-day mortality rate was 3.9% in patients who had cholecystectomy in an emergency setting while 2.6% represented the mortality rate of the whole cohort. We added the correct references in the discussion.

This imposed the readers an effort to read. The authors should provide concrete numbers from cited references. There was a difference between the conclusions stated in the abstract and those in the main text, making it difficult to understand the authors' assertions.

Authors’ reply: Thank you we corrected the abstract and main text.

Reviewer #2:

The complications of cholecystectomy were involved in this paper, but what complications, number of cases and causes were not analyzed?

Authors’ reply: As this study was focused on the decision-making process leading to the cholecystectomy we did not focus on the type of complications. However, we agree with the reviewer that it would be of interest reporting the type of complications occurred this was added in the text.

2. In terms of statistical methods, this paper analyzes the risk factors of symptomatic gallstone disease in elderly patients after cholecystectomy, but the classification of factors was obviously not detailed enough. For example, the postoperative prognosis of patients older than 80, 85 and 90 was different. In addition, the standard statistics on multivariate analysis needed to use logistic regression analysis and other analysis methods, which was not involved in the paper.

Authors’ reply: Logistic regression analysis was performed and detailed in the material and methods section. We also added 2 years follow up details to give a clearer view of the prognosis of these patients.

Reviewer #3:

1. Specific Comments to Authors: I would like to thank you for the opportunity to review

this paper. The topic is important and frequently encountered in clinical practice and I would like to congratulate the authors for the manuscript. There are several aspects to discuss: 1. All patients that were included in this study were symptomatic. There were 90 patients that were operated as elective cases. Can you describe patient's selection policy for surgery?

Authors' reply: Thank you. We included patients' selection policy in Material and Methods

Do you have data of the symptomatic patients treated medically without surgery, follow-up, and outcome data?

Authors' reply: We do not have such data as the study protocol included only patients who had undergone surgical treatment.

2. Open approach (52 patients) was more common in the group with postoperative complications. Which criteria were used for the open surgery? Is there any bias selection for much sicker patients that end up with more frequently complications or the procedure itself (laparotomy) is more harmful to the patients? The same discussion remains regarding the postoperative deaths.

Authors reply: As already mentioned, the decision is the result of a multidisciplinary discussion aimed at offering the best treatment. However, it might be possible that in a 10 years long study period the indication might have varied across years. Still, it seems that only patients undergoing conversion to open surgery had a worse postoperative course according to literature.

3. It would be of help adding data regarding the difficulty of the operation and intraoperative complications. There were 160 patients with mild complications (Clavien-Dindo 1-2), 26 patients (C-D 3-4) and 7 deaths. Please add a table with full description of these complications including surgical or medical complications.

Authors' reply: In order to clarify numbers relatively to postoperative complications we added a Table in the text with details

4. Regarding the last analysis (Table 3): were included in the analysis in the postoperative complications group only grade 3-4 C-D? Or also patients that died postoperatively?

Authors' reply: In the multivariate analysis also patients who died postoperatively were considered (Clavien Dindo 5).

5. It was showed that bilirubin and choledocholithotomy were prognostic factors for severe complications (Table 3). Patients with concurrent gallbladder a CBD stones represent a different population compared to the gallbladder stones-only group. There were patients with preoperative ERCP (23 patients), intraoperative ERCP (28 patients) and choledocholithotomy (15 patients) Are these three groups comparable? When and why some patients had preop ERCP and other had intraop ERCP?

Authors' reply: As stated above, in our center elderly patients with cholangitis have been addressed to antibiotic therapy ± endoscopic/percutaneous biliary drainage since 2004. This is in line with TG18.

This policy justifies also the number of ERCP performed in the preoperative setting in our cohort.

However, it was not always possible to solve the clinical problem with one preoperative procedure and in those cases we chose to perform an intraoperative endoscopic “rendez vous”. When this was not sufficient, it could be followed by choledocholithotomy. This is also in line with TG18 where it is stated “If the underlying etiology requires treatment, this should be provided after the patient’s general condition has improved; endoscopic sphincterotomy and subsequent choledocholithotomy may be performed together with biliary drainage”.

In addition, our center is an HPB hub for the region and this allowed more complex cases to be centralized in our institution.

It would be of interest to have the similar analysis (Table 3) focused on the patients with concurrent CBD stones. Regarding the detrimental effect of choledocholithotomy: is the procedure or severity/duration of high bilirubin levels?

Authors’ reply: IN our cohort patients who underwent choledocholithotomy had a preoperative level of bilirubin under 8 mg/dl

6. The Methods and Results sections of the Abstract should contain more information. The Conclusion describes 9.7% severe complication without adding patients that died postoperatively.

Authors’ reply: Thank you. We did not consider mortality in that rate and we corrected it in 11.5%

(1) Science editor:

The authors presented a retrospective cohort study to perform univariate and multivariate analyses on octogenarian patients experiencing complications following cholecystectomies for symptomatic gallstone diseases.

In order to justify performing cholecystectomies for octogenarian patients with symptomatic gallstone diseases, the authors should compare the study group with a control group (either younger patients undergoing cholecystectomies or octogenarian patients receiving medical treatment).

Authors’ reply: As stated above, our study protocol did not include the need to have a control group as the aim of the study was to revise all octogenarians that had cholecystectomy and to find risk factors that could help surgeons in the decision process leading to both emergency and elective surgery in this particular population.

Neither NICE 2018 nor TG18 suggest an age cut-off to surgically treat symptomatic gallstone disease or cholecystitis, based on the literature reporting similar results between elderly and control groups. In addition, TG 18 recommend the most complex cases in those centers with best skills in HPB surgery (as it is our institution).

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However, we noted that few statements on the safety of cholecystectomy on octogenarians could not be done without a control group and we corrected them.

The details of the surgical and therapeutic endoscopic indications (cholecystectomy, choledocholithotomy, preoperative ERCP, and intraoperative ERCP) were not described as well as those of the complications.

Authors' reply: We added a paragraph on indications in material and methods. We also added a table to show all postoperative complications in detail.

The authors failed to provide adequate information from the references to show their surgical complication rate was acceptable.

Authors' reply: Thank you. We updated and tried to provide corrected references.

There are 35 references in this manuscript of clinical research. Less than 50% ($13/35 = 37.1\%$) of the cited references represent publications from the recent 5 years. The self-referencing rate is high (more than 3%; $2/35 = 5.7\%$).

Authors' reply: Thank you. This was corrected.

The figure legends should be provided in detail. The abbreviations should be annotated (ROC in Figure 1 and DCA in Figure 2). The abbreviations should be annotated in all three tables. The language quality is grade C. Please visit the following website for the professional English language editing companies that we recommend:

<https://www.wjnet.com/bpg/gerinfo/240>.

The “Core tip” section is missing. Please write a summary of no more than 100 words to present the core content of your manuscript, highlighting the most innovative and important findings and/or arguments. Please provide it after the “Key words” section.

The “Acknowledgements” section is missing, too.

As a retrospective cohort study, Copyright License Agreement and Biostatistics Review Certificate have been attached.

Please provide an Institutional Review Board Approval Form in English. Signed Informed Consent Form, Conflict-of-Interest Disclosure Form (ICMJE form) and STROBE Statement are missing.

The statistical methods need to be checked by a specialist biostatistician.

Finally, all the issues raised by the peer-reviewers should be addressed accordingly.

Authors' reply: Thank you we corrected all these technical aspects.