

Date: 5 February 2021

Re: Manuscript ID 62253: Elderly patients (≥ 80 years) with acute cholangitis have similar outcomes as non-elderly (< 80 years): Propensity score-matched analysis

Dear Editor-in-Chief and Reviewers,

We are thankful to you and the reviewers for the insightful critic and comments. We have enhanced the manuscript accordingly and enclosed below is the point-to-point response with the changes made in manuscript (highlighted red in manuscript).

Yours sincerely,

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Reviewer

I have read the article of Chan et al “Elderly patients (≥ 80 years) with acute cholangitis have similar outcomes as non-elderly (< 80 years): Propensity score-matched analysis” with great interest. It describes an important topic in management of acute cholangitis, namely whether age affects outcomes in acute cholangitis. The authors have included 318 elderly and 139 non-elderly patients in a retrospective analysis, and performed subsequent a propensity-score analysis on 122 matched patients. They conclude that mortality rates were similar between the 2 patient groups, before and after PSM, even when AC severity was worse in the elderly group (before and after matching). Length of hospitalization was significantly longer in the elderly group before matching, but was comparable after matching. These results clearly show that outcomes are comparable between $> 80y$ and $< 80y$ patients. The title and abstract reflect the main subject of the manuscript. The rationale for the study is clear and relevant. The inclusion of patients was adequate, following the Tokyo guidelines, and the statistical methods are solid.

Reply: We thank you for the compliments and we hope that we are able to address your concerns below.

Comment 1. Although mortality rates and LOS are comparable, the questions remains whether there were differences in morbidity outcomes, which also could impact prognosis. Unfortunately these were not collected.

Reply: Thank you for the comment. We agree that it would be value add to have details about direct morbidity of acute cholangitis (e.g. respiratory, cardiac, renal etc.) as well as ERCP procedure related morbidity (e.g. perforation, bleeding, pancreatitis etc.). This remains an

important limitation of our retrospective cohort case matched study. Though, mortality data gives some insight into clinical outcomes, missing information is material and we have included this as a limitation. “We also did not collect data on disease or procedure-related morbidity and causes of mortality”

Comment 2. At this moment an age > 75y could result in a change from mild severity AC to moderate AC when following the Tokyo guidelines, resulting in higher chance of undergoing early drainage. Could the authors comment on how their results affect application of the AC severity classification? Should age be dropped from the severity criteria or comorbidity added? Should elderly patients that are classified as moderate AC based on age be reclassified as mild AC? Why did the authors did not choose a cut-off of 75y, parallel to the Tokyo guidelines? Perhaps the authors could add this to the discussion, and reduce some other parts that are less relevant (for example part on PTBD).

Reply: These are important points and we thank you for bringing this up. In our opinion, these aspects deserve an editorial to shed clarity on existing lacuna in body of evidence. TG13/18 guidelines have a scope of refinement, and any refinement should be backed by data and that was the basis of conducting this study.

The reason for choosing 80 years as age cut-off (instead of 75 years as proposed by TG13/18) was also brought by another reviewer (Reviewer 1, Comment 2). Recent studies report the safety of ERCP in elderly patients using various age cut-offs (ranging from 80 to 90 years) to determine “elderly” [1-3]. In Singapore, society is ageing and we manage elderly population increasingly. In our study sample, there were many elderly patients. If we restricted the age cut-off to 75 years, our sample size would reduce by about 20% limiting the statistical power of results. A 1:1 propensity score matching will at best result in total n=192 (96 in each arm), compared to our

study (n=224 with 112 in each arm; despite having 139 patients who were <80 years old and 318 patients ≥80 years old). We agree that since TG13/18 used age-cut off of 75 years to define elderly, an ideal and fair study that makes a reference to TG13/18 guidelines should consider cut-off of 75 years. Thus, we have added this statement in our limitation: “Existing studies evaluating the safety of ERCP in elderly patients have used a variety of cut-offs for age, ranging from 80 to 90 years old [33-35]. In addition, use of 75 years as a cut-off will reduce our sample size and impact the statistical power of study (96 patients <75 years and 361 patients ≥75 years compared to 139 patients <80 years and 318 patients ≥80 years respectively).” We also believe that though this is a limitation of the study design, this should not impact the results as we have previously reported in acute hepatobiliary sepsis that outcomes are more determined by co-morbid conditions and not solely restricted to age difference. Based on our results, if patients who were ≥80 years have similar outcomes as those who were <80 years, it is very likely to be true if age cut-off of 75 was used. In addition, there are studies which have evaluated the use of a cut-off of 75 years as a predictor of mortality; for instance, Schneider et al demonstrated comparable mortality in patients <75 years compared to ≥75 years in AC (<75 years: n=24/678 (3.5%) vs ≥75 years: n=13/303 (4.3%), OR 1.2 (95% CI: 0.6-2.5), p=0.588) [4].

1. Tohda G, Ohtani M, Dochin M. Efficacy and safety of emergency endoscopic retrograde cholangiopancreatography for acute cholangitis in the elderly. *World journal of gastroenterology* 2016; 22(37): 8382
2. Katsinelos P, Paroutoglou G, Kountouras J, Zavos C, Beltsis A, Tzovaras G. Efficacy and safety of therapeutic ERCP in patients 90 years of age and older. *Gastrointest Endosc* 2006; 63(3): 417-423
3. Mitchell RMS, O'Connor F, Dickey W. Endoscopic retrograde cholangiopancreatography is safe and effective in patients 90 years of age and older. *Journal of clinical gastroenterology* 2003; 36(1): 72-74

4. Schneider J, Hapfelmeier A, Thöres S, Obermeier A, Schulz C, Pfürringer D, Nennstiel S, Spinner C, Schmid RM, Algül H, Huber W. Mortality Risk for Acute Cholangitis (MAC): a risk prediction model for in-hospital mortality in patients with acute cholangitis. *BMC gastroenterology*. 2016 Dec;16(1):1-8.

The question of removing age from the TG classification, addition of co-morbidities, re-classification of patients >75 years of age as mild AC and the impact of our results on the classification of AC severity is complex. Ideally a prospective multicentre study of adequate power need to be conducted. Reviewer 1 also raised similar comments (Comment 6) too and it shows the clinical importance of this issue. We agree that age may impact outcomes. In clinical practice, we observe that many elderly have good outcomes while patients who are relatively younger patients but with significant co-morbidity have inferior outcomes i.e. physiologic age versus actual age. Ageing is associated with reduced functional reserves even though patients may not have underlying co-morbidities. Thus, the impact of age is both dependent on as well as independent of co-morbidity. In our opinion, cumulative indices inclusive of multiple parameters (including age) may be better markers for severity stratification and outcome prediction. For example, Charlson comorbidity index is a predictor of disease severity on multivariate analysis in AC patients treated by ERCP [1]. Further studies need to be done to validate the impact of age on disease severity and clinical outcomes. Unfortunately, there is paucity of literature on AC in general with regards to clinical outcomes. In our opinion, though our study demonstrates that clinical outcomes in elderly >80 years are similar to non-elderly; elderly patients should continue to be risk stratified as moderate/severe AC as vigilance in clinical care is essential. We have summarized this in our discussion: “The important issue the surfaces from our study is, if age should be considered as part of a risk stratification tool for the severity of AC. Age is usually

included in severity classifications as a surrogate marker for functional capacity and extent of comorbidities. The use of other surrogate markers such as the clinical frailty scale or Charlson co-morbidity index may be a better predictor of disease severity in AC [48]. In reality however, age serves as a useful tool in view of its ease of use as well as age associated reduced functional reserves that are not associated with any co-morbidity. While clinical outcomes are not determined by age in patients with AC in our study; based on available literature, we advocate that age should continue to remain as one of the component variables that determines disease severity in patients with AC.”

We believe more evidence is needed before we could advocate for the removal of ‘age’ as a criterion for severity stratification for patients with AC. In addition, many validated and established scoring systems continue to include ‘age’ as one of the variables for risk stratification.

Comment 3. A larger proportion of elderly patients had a history of bile stone disease compared to non-elderly patients. Could it be that more elderly patients had a previous ERCP with papillotomy, thereby reducing complications compared to non-elderly patients?

Reply: Thank you for this question. It is true that ERCP papillotomy has been shown to reduce the risk of complications e.g. reducing risk of future cholangitis. Lee et al in 2007 who analysed 83 patients who had endoscopic sphincterotomy (vs 34 patients who did not) in patients with absent common bile duct stone shown on ERCP demonstrated a significant reduction in cholangitis recurrence for the endoscopic sphincterotomy group (HR 0.305, 95% CI 0.095-0.975, p=0.045) [1].

In our study about half of the patients had history of previous biliary disease and thus, this is an important consideration. We realized that we did not define our concept of biliary disease history, and hence we have added the following statement in methodology section – “Previous history of biliary colic, acute cholecystitis, AC, and acute biliary pancreatitis were collectively defined as history of biliary disease.” We did not collect separate data on each of the diagnosis and hence are unable to comment on how many patients underwent ERCP, and how many patients underwent papillotomy prior to current admission. From our experience, the incidence of asymptomatic cholelithiasis (with no previous endoscopic / surgical intervention) is definitely more common than patient with need for ERCP, and papillotomy is selectively done at ERCP. We have added this in discussion (limitations) section: “We also did not categorize which patients with history of biliary disease had prior ERCP and papillotomy. It is possible that elderly patients were more likely to have prior ERCP and papillotomy, and this could impact results of our study.

1. Lee SH, Hwang JH, Yang KY, Lee KH, Park YS, Park JK, Woo SM, Yoo JW, Ryu JK, Kim YT, Yoon YB. Does endoscopic sphincterotomy reduce the recurrence rate of cholangitis in patients with cholangitis and suspected of a common bile duct stone not detected by ERCP?. *Gastrointestinal endoscopy*. 2008 Jan 1;67(1):51-7.

Science Editor:

1. The authors limited the inclusion criteria to choledocholithiasis. This needs clarification and clearly impacts the generalizability of the results. The questions raised by the reviewers should be answered

Reply: Many thanks for asking us to clarify our inclusion criteria with restriction to ‘stone’ disease and exclusion of ‘non-stone related’ acute cholangitis. Majority of non-stone related cholangitis are due to malignancy. In clinical experience, management and prognosis of patients with stones is different than malignancy and to group the two together would significantly impact the results. Thus, restriction in inclusion criteria was essential to ensure results remain valid for calculous acute cholangitis. We have clarified this also in reviewer response.

2. I found no “Author contribution” section. Please provide the author contributions

Reply: Thanks. We have provided the author contribution section in the Title page.

3. I found the authors did not provide the original figures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor

Reply: We have uploaded the figures onto PowerPoint. However, please note that Figure 2 was made using R software and hence is not editable nor can be reprocessed by any image editor. We hope that this is acceptable.

4. I found the authors did not write the “article highlight” section. Please write the “article highlights” section at the end of the main text

Reply: We have included the “article highlight” section at the end of the article.

5. There are 11 self-citations. The manuscript could only have 3 self-citations according to the editorial policy of BPG.

Reply: Many thanks for this comment. It is not our intent to self-cite without good necessity. We have identified citations 4,10,13,15,23,28,39,41,42,46 and 47 as the eleven self-citations. Some of the citations, though they are self-citations, are material in the context of this paper. The Senior Author (VGS) has extensive interest in acute care biliary surgery and thus he has done substantial work in this area. Hence, some of the self-citations are inevitable. However, we have made a careful consideration of BPG editorial policy and we decided to trim 3 citations (citations 28, 42 and 47). The details are as below.

Citation 4 – is in relation to frailty, sarcopenia, prehabilitation protocol and is a review paper that is quoted to support the issues faced by elderly. We consider it appropriately cited.

Citation 10 – Is an experience of elderly patients with CBD exploration to support that outcomes of elderly are non-inferior in biliary surgery. We consider it appropriately cited.

Citation 13 and 15 – These are both local experiences too. Citation 13 supports that age doesn't determine clinical outcomes and citation 15 supports that age determines LOS. If Science editors accepts this, we request to keep these two citations also as it is within the scope of our paper.

Citation 23 - Senior author, Dr Vishal, is a part of WSES (World Society of Emergency Surgery) committee guidelines and thus we request that Citation 23 (Sartelli M, Weber DG, Ruppé E et al. Antimicrobials: a global alliance for optimizing their rational use in intra-abdominal infections (AGORA). World Journal of Emergency Surgery 2016; 11(1): 33 [DOI: 10.1186/s13017-016-0089-y]) not be considered as a self-citation.

Citation 28, 42 and 47 – We find these citations relevant, however we have decided to omit them as they are not pertinent. Citation 28 is on the management of perforated peptic ulcer, citation 42 is on the impact of microbiology on pyogenic liver abscesses and citation 47 is on risk stratification in acute pancreatitis. These papers are cited in appropriate clinical context, but may be considered as not directly relevant for acute cholangitis and thus, we have decided to omit these citations.

Citation 39 – This is a book chapter on Acute Cholangitis. We request to allow us to keep it. It is a comprehensive review on acute cholangitis.

Citation 41 – This is in relation to microbiology and we are already omitting citation 42, may we also request to allow us to keep as it is important to let readers know about the importance of fungal infections in biliary system too and the impact on clinical outcomes.

Citation 46 – This paper concluded that index admission treatment is not only cost effective but also improves quality of life. We are omitting 47 citation and thus we request to keep citation 46.

Please consider this.

Please take note that after the removal of the 3 self-citations

Date: 17 March 2021

Journal Editor-In-Chief's Review Report

Re: Manuscript ID 62253: Elderly patients (≥ 80 years) with acute calculous cholangitis have similar outcomes as non-elderly (< 80 years): Propensity score-matched analysis

Dear Editor-in-Chief,

Thank you for your comment to further enhance our manuscript. We have made amendments to the manuscript under “tracked changes”

Please take a look at our response to your question: The overall in-hospital mortality, 30-d mortality and 90-d mortality was 4.6%, 7.4% and 8.5% respectively. This is pretty high. Is the cause of mortality related to the ERCP or underlying disease? If it is available, adding the cause of mortality will give higher impact of this paper.

Response: Thank you for this question. We have added in the following response into the manuscript under “tracked changes”.

Our reported mortality is comparable to mortality of less than 11% cited in more recent studies^[28,29]. The higher mortality compared to some reports may be due to advanced age or co-morbidity associated with ageing^[30]. With regards to the exact cause of mortality, we did not collect separate data, and this remains a limitation of our study. However, locally, our institution tracks procedure-related mortality separately; ERCP-related mortality is $<1\%$ locally. Further, it is difficult to distinguish ERCP-related complications such as post-ERCP cholangitis from the

index-admission sepsis. Due to the retrospective nature of our study, it is difficult to establish a cause-effect relationship.

Yours sincerely,

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