Author’s response to reviews

Title: Outcome comparison between percutaneous cholecystostomy and cholecystectomy: a 10-year population-based analysis

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Author’s response to reviews:

Dear Editor,

Attached please find the revised manuscript entitled “Outcome comparison between percutaneous cholecystostomy and cholecystectomy: a 10-year population-based analysis” (BSUR-D-17-00262R2) for your consideration for publication in BMC Surgery. This manuscript was carefully revised according to the suggestions from the editor and reviewers. We are grateful for all the comments, which have helped us improve the overall quality of the manuscript. Our point-by-point responses to the editor’s and reviewers’ comments are listed below, with detailed explanations.

We look forward to hearing from you.

Sincerely,

Corresponding author

K. Robert Lai, Professor

Yuan Ze University, Taoyuan, Taiwan
Point-by-point response to reviewers’ comments:

Editor - general comment:

I believe that the revised manuscript is much improved and deserves publication on BMC. Still, I am concerned with some aspects. In particular there is now a mismatch between your data and the new conclusions. Your new table 4 clearly shows that mortality is higher in PC than in CCS as a whole and also in all subgroup analysis. This is the most valuable finding of your study. However, your conclusions seem to go into a different direction. As before, I provided you with a more detailed commentary in a separate peer review that you can find below.

Response: Thank you for the helpful suggestions. We have modified the conclusion, and it should now match the data. Our responses to all specific comments are provided in detail below.

Reviewer 3 (Editor: Fabio Cesare Campanile, M.D.) general comment: I would like to congratulate you for the impressive dataset and the excellent work of revising the previous manuscript. I think that the paper is now substantially improved. In particular, the new table 4 presents unique data that certainly deserved publication and, in my opinion, well contribute to the understanding of the role of percutaneous cholecystostomy.

Response: Thank you.

Still, a few remarks are necessary and a few further revisions could add more value to the paper. I will start with the most trivial to finish with what I believe is the main methodological critical aspect, that concerns the new conclusions

1. p. 6 lines 17-20 (the reference is to the numbers on the left column of the pdf, it corresponds to the 6th line of the "Data Definition" paragraph): "When patients initially had undergone PC before CCS, they were classified as PC patients, and the reverse was also true" I do not understand how a PC can be carried out on a patient who already had the gallbladder removed by a CCS. Probably you did not mean it.
Response: We have modified the definition as follows: “When patients initially underwent PC, they were classified as PC patients. Similarly, patients were classified as CCS patients when they initially underwent CCS.” (Please also see the Data Definition section, lines 17-20 on page 7, of the revised manuscript.)

2. p. 12 line 28: "Fabio et al. [28] conducted a survey of the literature..."; I really appreciate your acknowledgement of this paper; please note that the correct mention of it should be "Campanile et al. [28] conducted a survey of the literature..."

Response: We apologize for this error and have corrected it. (Please also see the Discussion section, lines 25-31 on page 13, of the revised manuscript.)

3. In table 4, legend should be specified that the relative risk is expressed in Odds ratio.

Response: Thank you for the advice. The relative risk is expressed as an odds ratio in Table 4.

4. In the methods section: "30-day mortality referred to patients who died within one month after discharge, and did not include the patients who died during hospitalization”. The current definition of 30-day mortality includes, and not excludes the patients who died during hospitalization, as in your original version. My remark #5 only meant to bring your attention to the fact that your reported definition was mis-typed, not that it was wrong. I am sorry I was not clear enough! In other words, you had given the same definition ("patients who died during hospitalization") to both your indexes, but, of course, it was a simple writing mistake. In your table 4 the use of the correct 30-day mortality (i.e. with the inclusion of the patients who died in the hospital) would make clearer your results and more evident the difference in risk between the two procedures.

Response: We apologize for the misunderstanding. The dataset in the present study is inpatient data, which contain only admission and discharge dates and do not have the patient’s specific surgical time; therefore, we cannot infer the exact 30-days after operation. Due to the limitation of our dataset, we used the variable “30-day mortality after discharge” to replace “30-day mortality”, which was defined as follows: “30-day mortality after discharge referred to patients who died within 30-days after their discharges.” (Please also see the Measurement Outcomes section, page 8, lines 39-40 of the revised manuscript). The variable of “30-day mortality after discharge” does not include patients who died during hospitalization. Therefore, to clarify our results and make the difference in risk between the two procedures more evident, we also defined a new variable, “Total mortality”, to calculate the combination of “30-day mortality after discharge” and “in-hospital mortality”, which we defined as follows: “Total mortality was
calculated by including both of the cases died in the hospital and those who died within 30-days after their discharges.” (Please also see the Measurement Outcomes section, page 8, lines 42-45 of the revised manuscript.)

We also recalculated all variables, according to the new definitions, in Table 2 and Table 4.

5. Your data show, more clearly than in any other paper in the literature, that the mortality risk is far higher for PC than CCS, even if examined in subgroups stratified by age or co-morbidity and cause of procedure. I think that this is the most valuable finding of your study and it should be emphasized. PC carries a mortality risk that is increased from a minimum of 1.4 fold to a maximum of 34.2 fold. Even in the most serious scenario (patients of age 70 or more with a CCI>3 and an acute cholecystitis) the CCS, when possible, carries a lower risk of death. But your conclusions are not consistent with your own data and I believe that some methodological aspect should be underlined. In fact, in the conclusions (and in the discussion on p. 13) you state "However, due to the general conditions were far worse in the average PC patients than in the average CCS patients". Unless I misunderstood the data, your results are stratified by general conditions as far as possible; I do not understand the assumption that the average general condition were different between the two groups. Of course, you acknowledge that the particular dataset you worked on may not disclose complete details on the patient general conditions (and this should be stated in the "discussion" limitations section) but still, to the best of your knowledge, the patients are grouped in rather homogeneous groups (for example patients with CCI score of 3 or more) and the comparison of those homogeneous groups shows that PC mortality is worse. Furthermore, "some patients who underwent PC could not have tolerated any surgery" this is an important selection bias that has to be specified in the limitation section; but, again, this bias alone cannot justify a conclusion that appears to be contradictory with the data ("so we could not conclude that PC was inferior to CCS based on a simple comparison"), certainly you are right to be cautious, but your data are something more than a simple comparison and you should really stand up by them and conclude that, based on your data, PC is not as safe as suggested and actually its mortality rate is higher than CCS.

Response: Thank you for the valuable suggestion. We have modified the Conclusions section to be consistent with the data in Table 4, as shown below. (Please also see the Conclusions section, lines 39-59 on page 16, and lines 1-7 on page 17, of the revised manuscript.)

“Furthermore, the subset analyses demonstrated that the mortality rates were far higher in the patients who underwent PC than in the patients who underwent CCS in all subgroups, even in the worst scenario (elderly patients with AC and a CCI score of 3 or more), but the gap of the mortality rates between PC group and CCS group narrowed as the patients aged and with the seriousness of the diseases increased. The Tokyo guidelines considered the use of PC mandatory
for "severe" cases and strongly suggested that this procedure be used even in most moderate-grade cholecystitis cases; however, the present study determined that the role of PC in the Tokyo guidelines may be overstated. It is not as safe as the Tokyo guidelines suggested in moderate-grade cholecystitis cases, and it should be limited only to elderly and sicker patients. But still, as medical technology has improved, the mortality rates of PC have decreased, and the aging population has increased, we suggest strengthening and paying more attention to the use of PC technology in elderly and seriously ill patients.”

We have also modified the Discussion section, as shown below. (Please also see the Discussion section, lines 58-59 on page 13, and lines 1-26 on page 14, of the revised manuscript.)

“The results are shown in Table 4. The mortality rates were far higher among patients who underwent PC than among patients who underwent CCS in all subgroups, which increased from a minimum of 1.45-fold to a maximum of 34.22-fold. Based on the subset analyses, we conclude that PC is not as safe as the Tokyo guidelines suggested in moderate-grade cholecystitis cases and actually its mortality rate is higher than that of CCS, even in the worst scenario (elderly patients with AC and a CCI score of 3 or more) and that the relative risk of death for PC is 1.45-fold higher than that for CCS. We also found that the gap of the in-hospital and 30-day mortality after discharge rates narrowed as the patients aged and with the seriousness of the diseases. In other words, the relative risk of death is higher in less compromised patients but lower in the most serious patients. This important aspect means that PC should be limited only to elderly and sicker patients because in all other patients, the risk seems to be excessive.”

In addition, the “limitations” in the Discussion section for patient general conditions have been also modified as follows: “First, we could not obtain complete details on the general conditions for all patients due to the limitations of the data, which made it difficult to accurately determine the illness severity and thus made it difficult to group the patients in homogeneous PC and CCS groups. However, to the best of our knowledge, the results concerning the relative risk of mortality are stratified by the patients’ general conditions, to the greatest extent possible, including sex, age, cause of procedure and CCI score groups.” (Please also see “Limitations” in the Discussion section, lines 56-59 on page 15, and lines 1-9 on page 16, of the revised manuscript.)

6. P 16 lines 28-34: "Therefore, we posit that being elderly and critically ill may cause patients to be more likely to die during hospitalization or within 30 days after both types of operations and that the operation itself may not play a major role as a cause of death" Of course being elderly and critically ill increase your mortality. Still, even in the worst scenario (elderly patients with acute cholecystitis and a CCI score of 3 or more) you show that RR of death is 1.4 fold higher for PC. I do not think that a role of the operation itself can
be excluded. Your data show that that role is real (of course after consideration of all the possible limitations of your dataset).

Response: Indeed, we should follow the results shown by the data. Therefore, we deleted the hypothesis “and that the operation itself may not play a major role as a cause of death”. Then, we modified the sentence as follows: “Moreover, a large number of these patients generated a CCI score of 1 or more (61.14% after PC and 60.18% after CCS), which indicates that being elderly and critically ill may cause patients to be more likely to die during hospitalization or within 30 days after discharge for both types of operations.” (Please also see the Discussion section, page 14, lines 31-40 of the revised manuscript.)

7. "The Tokyo guidelines considered the use of PC mandatory for "severe" cases and strongly suggested the use of this procedure even in most moderate-grade cholecystitis cases; our study confirmed that the Tokyo guideline recommendations were adequate and current." You correctly state that the Tokyo guidelines suggested the use of PC even in most moderate grade cholecystitis. This corresponds to those patients with acute cholecystitis without organs/systems dysfunction. The group includes most of the patients with AC and CCI of 0; their relative risk (PC Vs. CCS) must be rather high, according to your data. Even the RR of the "severe" group (AC + CCI of at least 1) cannot be disregarded. Do you think that your data support the conclusion that the Tokyo guidelines are adequate and current. It appears to me that your paper is particularly interesting also because it is the first clear evidence that the role of PC in the Tokyo guidelines is overstated.

Response: Many thanks for the valuable suggestion. We have modified the conclusion as follows: “The Tokyo guidelines considered the use of PC mandatory for "severe" cases and strongly suggested that this procedure be used even in most moderate-grade cholecystitis cases; however, the present study determined that the role of PC in the Tokyo guidelines may be overstated. It is not as safe as the Tokyo guidelines suggested in moderate-grade cholecystitis cases, and it should be limited only to elderly and sicker patients.” (Please also see the Conclusion section, lines 50-59 on page 16, and lines 1-7 on page 17, of the revised manuscript.)

8. The in-depth subset analysis very interesting as it shows that gap between the in-hospital and 30-day mortality rates narrowed in the most compromised patients. The relative risk of death is higher in the less compromised patients (or, if you prefer, lower in the most serious patients). This important aspect means, in my opinion, that the indication for PC should be limited only to the sicker patients, because in everybody else the risk seems to be excessive.
Response: Thank you for the valuable advice. We have modified the contents as follows.

In the Discussion section (please also see lines 14 to 26 on page 14 of the revised manuscript):

“We also found that the gap of the in-hospital and 30-day mortality after discharge rates narrowed as the patients aged and with the seriousness of the diseases. In other words, the relative risk of death is higher in less compromised patients but lower in the most serious patients. This important aspect means that PC should be limited only to elderly and sicker patients because in all other patients, the risk seems to be excessive.”

In the Conclusion section (Please also see the Conclusion section, lines 50-59 on page 16, and line 1 on page 17, of the revised manuscript):

“The Tokyo guidelines considered the use of PC mandatory for "severe" cases and strongly suggested that this procedure be used even in most moderate-grade cholecystitis cases; however, the present study determined that the role of PC in the Tokyo guidelines may be overstated. It is not as safe as the Tokyo guidelines suggested in moderate-grade cholecystitis cases, and it should be limited only to elderly and sicker patients.”