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 Reviewers:

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

We look forward to hearing from you.

Sincerely,

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Point-by-point reply to reviewers’ comments:

Response to Reviewer 1:

Cholecystectomy is recommended as the first-line treatment for gall-stone, and percutaneous cholecystostomy is an alternative one in patients with poor risks for complications. The authors compared these two treatments on the hospital stay, costs, mortality and so on by nation-wide study containing 236,742 patients. Although the data is reliable owing to the large number of patients, unfortunately, it is hard to understand the aim authors focused on.

There are several questions and suggestions for corrections.

1) PC and CCS are essentially different treatments; PC is a palliative treatment for acute cholecystitis, while CCS is radical for gall stone. Therefore, it is meaningless to compare these methods.

Ans. We thank the reviewer for this question, which caused us to re-think our manuscript and make improvements. In terms of treatment procedures and techniques, PC and CCS are indeed different treatments; however, both of these techniques are treatments for diseases of the gallbladder. Although the mainstay of therapy for acute cholecystitis is CCS, the morbidity and mortality rates are high in elderly patients and in those with co-morbidities at the time of surgery [1, 2]. Therefore, the panel of the Tokyo guidelines states that this procedure is a safe option for critically ill patients, and the guidelines consider PC mandatory for patients with the severe grade of acute cholecystitis. The use of PC is also suggested for patients with moderate-grade cholecystitis [3, 4]. Additionally, this study is not the first to compare the outcomes of PC and CCS surgery. Numerous epidemiological studies have compared the health outcomes of PC and CCS based on hospital-level patient data [5]. For instance, Anderson et al. [6] conducted a nationwide examination of the outcomes of PC compared with CCS for acute cholecystitis in 2013. To the best of our knowledge, this report is the second population-based study to compare PC and CCS outcomes; thus, we believe the present study is interesting and useful.

References:


2) The article is too redundant and complex, and is hard to read.

Ans. We thank the reviewer for noting the problems with our manuscript. We have carefully revised the manuscript to ensure that the entire article is more readable. For example, the Results section is shorter and more concise now.

3) Finally, what is the purpose of this study?

Ans. The purpose of this study is as follows, which we have stated in the Background section (page 4, lines 28 to 59, and page 5, lines 1 to 12).

Purpose of this study: The controversy over the role of PC is fed by the absence of reliable data concerning its outcomes, and many authors maintain that there is no evidence to support the recommendation of PC over CCS in elderly or critically ill patients with AC. Additionally, the Tokyo guidelines, which were first published in 2007 [3] and then updated in 2013 [4], consider the use of PC mandatory for "severe" cases and strongly suggest the use of this procedure for even most moderate-grade cholecystitis cases. However, we could not determine whether the Tokyo guideline recommendations were adequate and current or whether they should be revised due to the lack of large amounts of data. Therefore, in-depth population-based research and analyses on the potential roles of PC in the management of AC and other gallbladder diseases are needed, which may lead to treatment suggestions for medical research institutions and surgeons for decision making concerning the management of patients with AC and the judicious use of PC and CCS. This study provides a relevant contribution to our understanding of the role of PC in the management of AC.
References:


Response to Reviewer 2:

The manuscript is well-written. Very impressive number of patients.

Ans. We appreciate your affirmation of the manuscript.

I would advise to:

- Revising the result section: making it shorter and more concise.

Ans. We thank the reviewer for the valuable comment. We have performed a substantial revision of the Results section, which is shorter and more concise than the original section.

- Always use absolute numbers in addition to percentages.

Ans. Thank you for your reminder; we have modified the numbers as follows.

In Results section, 1st paragraph (page 9, lines 25 to 28):

From 2003 to 2012, a total of 236,742 patients had undergone PC or CCS. Among them, 11,184 patients (4.72%) underwent PC, and the remaining 225,558 patients (95.28%) underwent CCS.

Table 3, 2nd Column:

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<tr>
<td>225,558</td>
<td>95.28%</td>
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<tr>
<td>11,184</td>
<td>4.72%</td>
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</table>
- Give some thoughts on clinical implications of your study

Ans. Thank you for this suggestion. We have added clinical implications to the Conclusions section (page 16, lines 36 to 50).

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. As medical technology has improved, the mortality levels of PC have decreased, and the aging population has increased; thus, we suggest strengthening and paying more attention to the use of PC technology in elderly and seriously ill patients according to the Tokyo guidelines.

- Illustrate (in a figure) how the proportion of drainage vs resection changed in the time period

Ans. Many thanks for the valuable suggestion. We have illustrated how the proportion of drainage vs resection changed during the time period in the Results section (page 9, lines 39 to 45) and Discussion section (page 11, lines 31 to 40).

Response to Reviewer 3:

Fabio Cesare Campanile, M.D. (Editor as Reviewer 3): The manuscript reports a very large population-based comparison between percutaneous cholecystostomy and laparoscopic cholecystectomy. The topic is very interesting and it became very relevant after the Tokyo guidelines, first in 2007 and then in 2013, considered the use of percutaneous cholecystectomy mandatory in the "severe" and strongly suggested even in most moderate grade cholecystitis. The controversy about the role of percutaneous cholecystostomy is fed by the absence of reliable data about its outcomes and many authors maintain that there is no evidence to support the recommendation of PC rather than cholecystectomy in elderly or critically ill patients with acute cholecystitis. This study can give a relevant contribution to our understanding of the role that percutaneous cholecystostomy may play in the management of the acute cholecystitis.

Ans. We thank the reviewer for the helpful comments. Our responses to all specific comments are provided in detail below.
The manuscript is well written. However, some remarks are necessary:

1. The introduction correctly delineates what is known about the topic. However, the role that the Tokyo guidelines attributed to the percutaneous cholecystostomy (not only as an alternative procedure in critically ill patients but even as a bridge to surgery in the moderate grade) and the related controversy in the literature should be described.

   Ans. We thank the reviewer for the valuable comment. We have added the role of the Tokyo guidelines attributed to percutaneous cholecystostomy and have described the related controversy in the literature in the Background section (page 4, lines 20 to 45).

2. The authors describe the need to "conduct in-depth population-based research...for Asian population"; however, even in the Western population only one large registry study compares percutaneous cholecystostomy and cholecystectomy.

   Ans. Thank you. We have modified the description as follows: “in-depth population-based research and analyses must be conducted to investigate possible roles of PC in the management of AC and other gallbladder diseases” (page 5, lines 1 to 6). Thus, the modified manuscript is no longer confined to the study of only the Asian population.

3. The research question could be better explained at the end of the introduction. Here, the aim of the study appears to include the comparison of the two procedures outcomes and not only its extension to the Asian population.

   Ans. We thank the reviewer for the valuable suggestion. We have modified the description of the research question at the end of the Introduction section (page 5, lines 1 to 12).

4. In the methods section (Data definition paragraph) it is not clear what is the meaning of the expression "first relevant operation". Do the authors mean the actual first operation received by the patient or there is the possibility that the first PC or CCS was considered "not relevant"? And what about the sentence "When patients had undergone PC and CCS as first relevant operation"? Of course, if they received one of them could not had the other at the same time.

   Ans. The word ‘relevant’ here is superfluous and can lead to misunderstandings; therefore, we have this term and modified the expression as follows: “We divided patients who accepted either
of the above two operation procedures into PC and CCS patients based on the first operation that
they received during their hospital stay.” (page 6, lines 12 to 17).

Concerning the question "When patients had undergone PC and CCS as first relevant
operation?": Generally, it is true that patients cannot undergo the two operations at the same
time. However, PC may be used as a bridge to CCS surgery during a same hospital stay in some
cases. According to our dataset, when the surgeons performed PC and CCS during the same
hospital stay, the CCS operation was performed last; because the prognosis was determined by
the CCS surgery, we classified this patient group as CCS patients. To avoid misunderstanding,
we modified the sentence as follows: “Patients who underwent both PC and CCS operations
during the same hospitalization (i.e., PC as a bridge to CCS surgery) were classified as CCS
patients” (page 6, lines 20 to 23).

5. In the "Measurement Outcomes" I find: "Thirty-day mortality was used to refer to patients
who died within one month after undergoing AC or CCS. This designation refers to patients
who died during hospitalization. In-hospital mortality was used to refer to patients
undergoing PC or CCS who died during hospitalization." I believe that only the "in-hospital
mortality" refers only to patients who died during hospitalization. In other words, "In-
hospital mortality" is the portion of "30-days mortality" occurred before discharge. This
could be a typo.

Ans. Thank you very much for the reminder. We modified the definition as follows: “30-day
mortality referred to patients who died within one month after discharge, and did not include the
patients who died during hospitalization.” (page 7, lines 39 to 42). We also recalculated all of the
30-day mortality rates according to the new definition.

6. A large part of the "results" section (and, again, in part of the discussion) actually repeats the
data already shown in the tables. The entire section could be more readable if a proper
reference to the appropriate table is done in the text, avoiding the redundancy.

Ans. We have modified the Results and Discussion sections carefully to make them shorter and
more concise. We have also referenced the tables in the text appropriately to avoid redundancy.

7. This is my main concern: the controversy about the role of the percutaneous gallbladder
drainage is based on the opinion, expressed by some of the authors (Winbladh et al published
the nice review on this particular aspect mentioned at reference #7) that the mortality is far
higher after PC than CCS, even for critically ill patients. This aspect is difficult to study
because the general conditions are far worse in the average PC than CCS patient and a proper
statistical comparison is impossible. In this study, the authors have the data about the severity of the illness of their patients and they can stratify their population by age, causes of procedure and CCI score. However, they use this stratification to compare costs and LOS (see table 4) but not morbidity and mortality. In Table 2 only the mean values for the entire, unstratified, population are given. This very large study could greatly improve its value if the authors could provide us with data comparing the morbidity and mortality of patients divided in age, causes of procedure and CCI score groups: it would be of the utmost importance to know if the morbidity and mortality of patients with acute cholecystitis and CCI 3 or higher (or those older than 70) is actually higher in those who underwent PC Vs. CCS or vice-versa. I think that the addition of the subsets analysis could justify a revision of the paper in order to further improve its interest. As a matter of fact, if we are able to prove that mortality is higher in PC or CCS, in the selected group of critically ill patients we could determine if the Tokyo guidelines recommendations are adequate and current or should be revised.

Ans. Thank you very much for your valuable suggestion.

We investigated the relative risk of death among patients who underwent PC versus patients who underwent CCS stratified by sex, age, cause of procedure and CCI score group; the results are shown in Table 4. To make the article more focused and concise, we deleted the stratified comparison of costs and LOS, which was shown in Table 4 in the previous version.

As shown in Table 4, the in-hospital and 30-day mortality rates were higher for PC than for CCS in all subgroups, and the in-hospital and 30-day mortality rates had similar distributions for each variable. Moreover, the gap between patients who underwent PC and CCS narrowed in patients with older ages and more severe disease (Table 4).

Although the comparison of mortality rates between the PC and CCS subgroups showed that the relative risks were higher for PC than for CCS, this finding still does not prove that the mortality rate is higher in the patients who underwent PC than in the patients who underwent CCS in all circumstances. Because some patients who underwent PC could not tolerate any surgery, this limitation had to be considered [9]. Moreover, the general conditions were far worse in the average PC patient than in the average CCS patient. We could not obtain clinical data for all patients due to the limitations of the data, which made it impossible to distinguish the severity of the illness accurately and thus made a proper statistical comparison difficult. According to the overall trend that if the patients were elderly or more seriously ill, then the gap of the mortality rate would be smaller, we hypothesized that the mortality rate of PC and CCS would be much closer as the conditions of the two comparison groups became more similar, and the opposite trend might even occur. Additionally, we found that most patients with PC or CCS who died in-hospital or within 30 days after an operation were 70 years of age or older (73.3 ± 14.0 years old after PC and 70.5 ± 14.7 years old after CCS). Moreover, a large number of these patients generated a CCI score of 1 or more (61.14% after PC and 60.18% after CCS). Therefore, we posit that being elderly and critically ill may cause patients to be more likely to die during
hospitalization or within 30 days for both types of operations, and thus, the operation itself may not play a major role as a cause of death. (page 13, lines 14 to 59, and page 14, lines 1-4)

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. As medical technology has improved, the mortality levels of PC have decreased, and the aging population has increased; thus, we suggest strengthening and paying more attention to the use of PC technology in elderly and seriously ill patients based on the points of the Tokyo guidelines (page 16, lines 36 to 50).

8. In the discussion section the authors analyze the temporal trends of PC and CCS in Taiwan and found an increase of the PC administration by 18.34% per year from 2003 to 2012. They consider that the aging of the population is at the basis of such an increase. Do the author think that the publication of the Tokyo guidelines in 2007 have also affected this trend?

Ans. Many thanks for the valuable suggestion. As shown in Fig. 1, the incidence rates of CCS and PC present different trends. CCS showed an upward trend from 2003 to 2009 but a downward trend from 2009 to 2012. However, the incidence of PC showed an upward trend from 2003 to 2012. Therefore, we think that the publication of the Tokyo guidelines in 2007 may also have affected this trend (page 12, lines 6 to 15).

9. Among the limitations the authors may want to include the fact that their "readmission due to complications" analysis is limited to a 1 month period while it has been shown that acute or emergency cholecystectomy may be needed far beyond that limit.

Ans. According to our data, we can extend this period to 3 months to meet the requirements of complication times for acute or emergency cholecystectomies. We have modified the definition of "readmission due to complications" as follows: "Readmission due to complications was designated when readmission occurred due to the diagnosis of a commonly encountered postoperative complication listed in Appendix A (Table 5) within 3 months after PC or CCS delivery" (page 8, lines 4 to 9). We have also updated the "readmission due to complications" results in Table 2.