Dear editor and reviewers:

At first, please allow me to thank you with all my heart for the chance of revising my manuscript. I learned a lot from your precious advice, which help me to consummate my research. I am submitting a revised version of our manuscript “Negative short-term impact of intraoperative biliary lavage in patients with hepatolithiasis”. In this revised version, I have addressed the concerns of the editor and the reviewers. Thank you for the helpful comments and suggestions.

I have revised the manuscript based on the suggestions and advice of the reviewers. An item-by-item response to their comments in enclosed. I hope that these revisions successfully address their concerns and requirements and that this manuscript will be accepted for publication.

According to the comments of the reviewers, we have made corrections and modifications as follows:

Reviewer 1:

This manuscript aims to answer an important clinical question when dealing with recurrent pyogenic cholangitis (RPC) - i.e. sepsis. There is no major flaw in statistical method and calculation. However, I would like to point out a few problems.

1. Firstly, the use of language which needs polishing.

   This manuscript was polished by a professional English language editor before the first submission, and the CERTIFICATE OF ENGLISH EDITING would be attached in the re-submitted profiles. We could request the language editor make a further modification to meet the publication demand.

2. In terms of background information of RPC, one major form of treatment - Hepaticocutaneous jejunostomy was not mentioned in the introduction of this manuscript.

   It was our mistake that we had ignored to describe the commonly used treatment options in the introduction section, such as hepaticocutaneous jejunostomy, endoscopic retrograde cholangiopancreatography (ERCP) with endoscopic sphincterotomy (EST), percutaneous transhepatic cholangioscopy (PTCS), etc.

We have added the appropriate content in the Introduction section. (In revision, Introduction Section, Paragraph 2nd, Line 5-8)

3. In addition, the operating surgeons for lavage vs. non-lavage group were different. I understand that this is a retrospective study but at least the authors should mention if the operating surgeons are of similar seniority so as to make the two groups comparable.

In our hospital, each chief surgeon, with his team, is responsible for the management of patients independently. Before becoming a chief surgeon (term leader), several strict conditions need to be met, one of which is at least 5-10 years career in corresponding professional field. In our department, all chief surgeons were engaged in hepatobiliary surgery more than 10 years. There were no difference in the evaluation of clinical assessment index among them annual. The operating surgeons in this study are similar seniority and skillful, so the result of the two groups are comparable.

We have added the appropriate content in the Materials and Methods section. (In revision, Materials and Methods section, Paragraph 3th, Line 3-6)

Reviewer 2:

This manuscript addresses the necessity and safety of intraoperative biliary lavage for hepaticolithiasis. This paper is interesting, but a substantial revision is needed to make this manuscript suitable for publication.

[Major]

1. About the treatment for hepaticolithiasis, transpapillary and percutaneous treatment are generally performed. You should mention the policy on treatment options for hepaticolithiasis in your institution.

Answer: In our hospital, the facilities and stuffs of ERCP/EST were administrated by Endoscopic Center, while PTCS/PTCD was running under the management of Department of Intervention, and both of the two departments were not belonging to surgery. Therefore, there were some difficulties in coordinating the various departments sometimes, eventually reached some consensus: EST was the primary treatment choice for extrahepatic bile stones, while all intrahepatic bile stones patients were resolved by

surgical procedure because only 2 out of 10 ERCP technicians were capable of removing the intrahepatic bile stones effectively. In addition, PTCS was implemented recently, so the patients were performed PTCS were not included in this study.

We have added the appropriate content (only the principle of treatment options) in the Materials and Methods section. (In revision, Materials and Methods section, Paragraph 3th, Line 1-3)

2. Therapeutic protocol is unclear. You mentioned “For patients with unilateral hepatolithiasis or with accompanying liver atrophy, liver resection was also performed during surgery” in Materials and Methods section, and “For the remaining 225 patients, the stones were located either on the left or right side of the liver only.” in Result section. I think these patients needn’t the intraoperative biliary lavage as the treatment. You should add the number of patients with unilateral hepatolithiasis in each group, and explain why intraoperative biliary lavage is necessary even for these patients, whose liver is finally resected.

Answer: Thanks for your advice. There are three reasons as follow for intraoperative biliary lavage is necessary even for these patients, whose liver is finally resected. First, hepatolithiasis is a benign progressive disease and some of these patients with varying degrees of liver cirrhosis. The process of liver fibrosis accompany with hyperplasia-atrophy of the liver tissue and even liver rotation that made abnormal anatomy. In addition, in order to protect liver function, we generally do not performed the expanded liver excision as malignant tumors, therefore, it has the potential risk of remnant lesions. Second, even if we complete resection of the lesion, the stones could be transportable, such as intrahepatic stones may be shifted to the extrahepatic bile duct, and therefore the rest of the biliary tract may exist stones still, for example, after the removal of the left lateral lobe, any of the left hepatic duct may exist residual stones, the use of intraoperative lavage can remove the stones. Finally, after the liver resection, the bile duct stumps on the plane of liver section need to be sewn up, while biliary lavage is an effective way to test the effect of the closure. Therefore, based on these three reasons, our department traditionally employed biliary lavage as a conventional method.

For these reasons, we considered that add the number of patients with unilateral

hepatolithiasis in each group was not significant meaningful, therefore, after this revision, we have not added the corresponding data. However, if the reviewer #2 still insist, I will add it in the follow-up work, thank you!

3. Compared to the control group, there were many liver cirrhosis patients who had impaired immune system in the lavage group. Can this fact cause the high incidence of the postoperative fever, cholangitis and abdominal infection in the lavage group? You should discuss this matter.

Answer: Thanks for your attention. We had not noticed the relationship between cirrhosis and infectious complications. In our study, each group of the hepatolithiasis patients have a various degrees of liver cirrhosis (71 (27.9%) vs 229 (33.8%)). As we all know, immune function would be impaired with liver cirrhosis, and therefore, cirrhosis may contribute to one reason of the postoperative fever, cholangitis and abdominal infection. However, in this study, liver cirrhosis between the two groups was not significantly different in statistical analysis (p=0.098), therefore, impaired immunity caused by liver cirrhosis does not affect our results.

We have added the appropriate content in the Discussion section. (In revision, Discussion section, Paragraph 2nd, Line 20-21)

4. Are there differences in the occurrence of postoperative fever, cholangitis and abdominal infection between open and laparoscopic surgery? Add the number of these patients in each group. If there is a significant difference, you should discuss this matter.

Answer: Thank you for your amendments, we have added the laparoscopic and open data in Table 2. There were 21 (8.6%) patients in Control group were performed by laparoscopic approach and 37 (5.5%) patients in Lavage group, while there was no significant difference between the two groups.

On the choice of surgical approach, the surgeon and patient took the decision together. In fact, there were several reasons that a lower proportion of laparoscopic surgery in this study. First, the majority of hepatolithiasis patients, with poor finance, were sensitive to the hospital fee. And laparoscopic operation may consume some more expensive equipment, which was not covered by medical insurance, so after we informed patients

the price difference between laparoscopy and open, most patients adopted open. Subsequently, in this study, 43.6% of patients had a previous history of biliary tract with tight abdominal adhesions, therefore, they are not suitable for laparoscopy.

[minor]

1. Table1, 2, 3, 4 and 5 are unclear for understanding the difference between the two groups. Add the proportion in each group.

   Answer: Thanks for your suggestion, we have added the proportion in each group in table 1-5.