Responses to reviewers' comments (Manuscript Number 28054)

The reviewers' comments have been helpful in allowing us to revise our manuscript. We have attempted to address the questions raised by reviewers as described below.

Responses to Comments of Reviewer 03488253

Q) Please define acute cholangitis better (fever + cholestasis lab parameters elevation).

A) In the "Definition" paragraph of the "Materials and Methods", we defined acute cholangitis as a fever of >38 °C that was thought to be due to a biliary infection (page 6, line 17-18). This definition was obscure, so we changed the explanatory note of acute cholangitis as follows:

Acute cholangitis was diagnosed as clinical symptoms characterized by a fever, jaundice, and abdominal pain that thought to be a result of cholestasis and bacterial infection in the biliary tract. Laboratory data indicative of the presence of inflammation (e.g., leukocytosis), biliary obstruction (e.g., hyperbilirubinemia, elevation of biliary and liver enzymes), and imaging findings supporting the evidence of inflammation and biliary obstruction were also used for a more accurate diagnosis of acute cholangitis (page 6, line 18-24).

A) In addition, we explained the diagnostic criteria of the severity of acute cholangitis as follows;

Severity of acute cholangitis can range from mild to serious life-threatening levels. We classified acute cholangitis into three grades; mild (grade I), moderate (grade II), and severe (grade III), in accordance with the Tokyo Guidelines[25], which have since been widely used all over the world as the diagnostic criteria and a severity assessment of acute cholangitis (page 6, line 24 – page 7, line 3).

Responses to Comments of Reviewer 02985786

Q) Was a power analysis done to determine the needed sample size? - this is a major problem. The authors do comment in the submission that underpowering may be a problem.

A) In this study, we have evaluated the efficacy and safety of interventional ERCP for patients with acute cholangitis. Based on this point, we have calculated the required sample sizes using *ESR* statistics software, and finally judged that the sample size in each group (60 cases of elderly group and 68 cases of control group) could seemed to be insufficient to make a definite conclusion.

Therefore, we prolonged the observational periods up to June 2008, and have collected an additional data of 79 cases with acute cholangitis requiring emergency ERCP (42 cases of elderly and 37 cases of control group). By providing power calculations for the modified sample size (102 of elderly group and 105 of control group), a two group chi-squared test with a 0.050 two-sided significance level will have 70% power to detect the difference between the elderly group and the control group. Finally, we have clarified that the modified sample size (207 cases) in the revised manuscript was sufficient in numbers to support our conclusion.

We added the following sentence: "We have confirmed that the sample size of each group in this study is sufficient in size to make a definite conclusion using power calculations" at the top of the Statistical analysis paragraph (page 8, line 14-15).

A) Reviewer said that the authors do comment in the submission that underpowering may be a problem. However, we don't mention such a comment in the discussion paragraph. In our manuscript, we only insist that low complication rates which are observed in this study may not hold true

because of the limitation of observational periods. This potential problem is completely different from the sample size.

Q) Was there any blinding of the personnel who reviewed the charts? Did one or more data collector review the charts? Was the data collection tool piloted and assessed for accuracy and precision?

A) In this study, two gastroenterologists (G.T and M.D) had reviewed the electronic medical charts and collected the data of all the patients involved. To the best of our knowledge, there was no blinding of the personnel who reviewed the medical charts. We had input the all data of the patients involved in this study into statistically analyses software *EZR* manually. We didn't use any types of data collection tools. However, the accuracy of the all data was confirmed through double checking.

Q) If more than 2 people reviewed the charts, how were disagreements handled?

A) There were no disagreements between the two gastroenterologists (as previously described) who had reviewed the electronic medical charts of all patients involved in this study.

Q) Was there any missing data and, if there was missing data, how was this handled?

A) Since April 2007, every case of acute cholangitis had been diagnosed and treated consistently according to the clinical pathway in our institution. Therefore, in all cases involved in this study, there were no missing data of blood test, medical history and details of endoscopic procedures.

Responses to Comments of Reviewer 3477256

Q) Hospitalization period was significantly increased in the elderly group (21 vs. 15 days). What was the reason for this observation?

A) In the submitted manuscript, we explain the accurate reason of a long hospitalization period in the elderly group as a following sentence:
The median duration of hospitalization periods was significantly longer in the elderly group than in the control group (21 days vs. 15 days) because many elderly patients required rehabilitation periods for improvement of their overall health and other conditions.

In our study, we judged the recovery of patients with acute cholangitis by the following conditions: (a) an improvement of clinical symptoms such as a fever, jaundice and abdominal pain, and (b) a normalization of laboratory data such as leukocytosis, hyperbilirubinemia and elevation of biliary enzymes. Between the elderly group and the control group, there was no significant difference of the recovery durations (8.5 days vs. 7.7 days). However, many elderly patients had decreased their physical activities due to hospitalization, and required rehabilitation to recover their abilities to move. As a result, a median hospitalization period became longer in the elderly group than the control group.

Q) Did any of the patients use NOAK? Did the authors observed any bleeding complications under NOAK?

A) In this study, 52 patients were taking anticoagulant or antiplatelet drugs. Among these, 7 patients were taking NOAC (Novel Oral Anti Coagulants) - 4 cases of Rivavoxaban and 3 cases of Dabigatran etexilate. For all 7 patients with intake of NOAC, endoscopic biliary drainage were performed as an initial ERCP, and 6 of them had endoscopic sphincterotomy (with or without stone removal) as an additional treatment. However, there were no bleeding complications after the endoscopic procedures.

Q) Serum amylase was determined after ERC/P. Why not Serum lipase which is more specific?

A) In our institution, it takes less than 1 hour to get the result of serum amylase. In contrast, it takes 1 day to get the result of serum lipase. Although we know that serum lipase is more specific than serum amylase to detect the evidence of acute pancreatitis, we have routinely checked serum amylase in order to judge the possibility of acute pancreatitis as quickly as possible. We evaluated the possibility of post-ERCP pancreatitis (PEP) by not only laboratory data (including serum amylase level) but also patients' physical conditions (fever, epigastric pain, back pain). If the patient with normal serum amylase level is suspected to be PEP by his or her physical condition, we additionally check serum lipase level. However, we haven't experienced such a case in our study.

Q) Did any of the patients receive rectal indomethacin prior to ERC/P?

A) It has been reported that pre-procedural administration of rectal indometacin could decrease the occurrence of post-ERCP pancreatitis (Gastroenterology 2016; 151: 288-297, Lancet 2016; 387: 2293-301). However, it's efficacy has still been controversial (Gastroenterology 2016; 150: 911-7). We insert prophylactic pancreatic stent in cases of gallstone pancreatitis, but don't use any types of rectal NSAIDs prior to ERCPs.

Q) Which antibiotic regime was preferred in both groups? Was it similar?

A) Since cefmetazole (CMZ) is stable to any type of bacterial beta-lactamases, and has broad spectrum antibacterial action for Escherichia coli, Klebsiella spp., Proteus vulgaris, and Bacteroides fragilis, we routinely used CMZ (3g/day) in the elderly and control groups, according to the clinical pathway in our institution.