

Reply to the reviewers' comments

Question Number	Original comments of the reviewer	Reply by the author(s)	Changes done on page number and line number
1	Usually, ES/EPBD are conducted in the patients with symptoms, thus what is the effect of cholelithiasis without symptoms on the cholangiocarcinoma ?	Chi-Chih Wang	Our data comes from national health insurance research database of Taiwan and this is a hospital based database. I think our data all comes from hospital base. We can only explain the effect of cholelithiasis with symptoms on cholangiocarcinoma.
2	2.How to illustrate that it is ES/EPBD or ES/EPBD's complication to impact the incidence of cholangiocarcinoma?	Chi-Chih Wang	Because of the study design, we noticed that patient suffered from choledocholithiasis underwent ES/EPBD having higher subsequent cholangiocarcinoma rate comparing to no intervention or cholecystectomy. But we don't know the impact of incidence of cholangiocarcinoma comes from ES/EPBD or its complication.
3	Does the level of severity of cholelithiasis impact the consequent incidence of cholangiocarcinoma? It is better to divide the patients to various group with different levels of severity	Chi-Chih Wang	We think the repeated cholangitis may influence the incidence of cholangiocarcinoma and we add the data of comparisons recurrent biliary events between cholangiocarcinoma patients and non-cholangiocarcinoma patients in ES/EPBD group. 16 patients who had cholangiocarcinoma within 6 months after cholelithiasis endoscopic treatment were excluded from further analysis because of possible miss diagnosis initially. (Results showed in supplementary table 2)
4	In Figure 2, cholecystectomy could decrease the incidence of cholangiocarcinoma through decreasing the requirement of ES/EPBD. Is it true?	Chi-Chih Wang	We found that in symptomatic cholelithiasis patients, cholecystectomy can reduce further cholangiocarcinoma incidence even comparing with no intervention group. We cannot sure that the cholangiocarcinoma incidence is lower in cholecystectomy group because of decreasing the requirement of ES/EPBD or the difference between cholecystitis and cholangitis.

5	As a retrospective cohort study, the prolonged time period may help to minimize the deviation. On the other hand, carcinoma needs time to develop. Thus it is better to prolong the observational period to 10-15 years.	Chi-Chih Wang	Because of the current finding of our results, we already started to initiate another larger scaled national wide health insurance data with follow up time expansion to 16-17 years, but this need a lot of efforts and support to complete this work. We also try to build up our own ERCP data base of one medical center. I hope our further work can clarify the mystery what we left now.
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