

Dear Dr. Yuan Qi, editor, and reviewers:

At first, please allow me to thank you with all my heart for the chance of revising my manuscript. We appreciate editor and reviewers very much for your positive and constructive comments and suggestions on our manuscript. We learn a lot from your precious advices, which help me to consummate my research. I am submitting a revised version of our manuscript entitled **“Prognostic Factors and Long-term Outcomes of Hilar Cholangiocarcinoma: A Single-Institution Experience in China” (Manuscript NO.: 23012)**. In this revised version, we have addressed the concerns of the editor and the reviewers. Thank you for the helpful comments and suggestions.

In response to comments from the editor, in your letter dated November 6th, 2015, you suggested to have the text edited by a native speaker with knowledge of medical English. According to your experiential advice, I have invited a native English speaker to examine the grammatical, spelling mistakes, and then polish it. We have studied reviewer's comments carefully and have made revision which marked in red in the paper. We deleted some repeated contents, such as results in the discussion section. Also, we delete some minor important contents. We have tried our best to revise our manuscript according to the comments. If this kind of revision is inappropriate, please put up your precious and professional suggestion, and we would revise it again.

We have revised the manuscript based on the suggestions and advice of the reviewers. An item-by-item response to their comments is enclosed. We hope that these revisions successfully address their concerns and requirements and that this manuscript will be accepted for publication. We would like to express our great appreciation to you and reviewers for comments on our paper.

Looking forward to hearing from you soon.

With best regards,
Fu-Yu Li

As for the comments of reviewers:

Reviewer #1 (02444986):

Authors retrospectively analyzed characteristic of 814 hilar cholangiocarcinoma (HC) patients from single center in China. They determined the prognostic factors for overall- disease free survival and R0 resection. Although the manuscript supplies very important demographic data for survival of HC patients, the only original finding of the analyses was that caudate lobectomy was a good prognostic factor. All other factors (tumor diameter, surgical procedures, AJCC T stage, vascular invasion) were expected ones.

(Q1) Although the study is retrospective, authors stated that “patients gave their informed consent statement prior to the study inclusion.

Answer: Thank you so much for reviewing our manuscript, we are terrible sorry for our little experience in preparing manuscript. In fact, when the patients were admitted into our hospital, before surgery or treatment, the patients and their relatives were being told that in the future they would be involved into a database and some of their data are likely to be used in clinical studies. And they agreed. So, as our study was a retrospective cohort study and the magazine required the informed consent statement of the patients or their relatives, and required us to write the sentence “patients gave their informed consent statement prior to the study inclusion” in the manuscript. And if it seems improper, I would revise it again. Thank you so much for your experiential advice.

(Q2) Tables are very confusing and they should be redesigned: Table 1: Values should be separately indicated as either number (%) or median [range]; male or female row should be omitted; preoperative laboratory data should be organized as tumor markers, liver tests (which must include total bilirubin as a well defined prognostic factor), etc.; type complications and surgical deaths were explained within the text, so should be omitted. Table 2 should be either omitted by giving data within text or integrated to Table1. Table 3 and 4 should be formatted as Table 5. Table 4 and 5 are respectively indicating multivariate analysis for survival and R0 resection. In order to avoid confusion, the title of table 5 should be changed as “multivariate analysis for risk factors for tumor free resection margin”.

Answer: Thank you very much for this comment. And I have already redesigned the tables, for table 1, Values have already separately indicated as either number (%) or median [range]; female row have already been omitted; preoperative laboratory data have already been organized as tumor markers and liver tests, and our manuscript

already have the total bilirubin level in our text, which was short for TB. Postoperative complications and surgical deaths have already moved from the table 1, we believed that table 3 is more concise and we have already moved the insignificant factors which was not associated with OS and DFS (the Bismuth-Corlett classification). And Table 4 was formatted as Table 5. Since factors listed in the tables may look more clear and concise, and it is difficult to integrated Table 2 into Table1, so I think table 2 can be retained. Table 5 has already been renamed as “**Multivariate analysis of risk factors for tumor free resection margin**”. And if it seems improper, I would revise it again. Thank you so much for your experiential advice.

(Q3) The important points should be emphasized within the text, instead of repeating the data given at table i.e “With regard to Bismuth-Corlette classification, 95 (25.2%), 92 (24.2%), 102 (26.8%), 92 (24.2%) patients with curative surgery were classified as Bismuth-Corlette type I, II, III, IV...Table1.” , “As was shown in table 3, OS was significantly longer in patients with no lymph node metastasis ($P<0.001$), well histological....

Answer: Thank you very much for this comment. And we have already deleted some repeated part in our text, we deleted: Results- Patients and Tumors – “**In the curative group, 231 patients were males and 150 patients were females with a median age of 60 years (range, 26-82 years). The most common clinical manifestation was painless jaundice in 267 patients (70.1%). With regard to Bismuth-Corlette classification, 95 (25.2%), 92 (24.2%), 102 (26.8%), 92 (24.2%) patients with curative surgery were classified as Bismuth-Corlette type I, II, III, IV tumors respectively versus 16 (4.8%), 59 (17.9%), 102 (30.9%), 153 (46.4 %) patients with palliative intent surgery classified as Bismuth-Corlette type I, II, III, IV tumors.**” Since the aim of our current study was to analyze the prognostic factors with OS and DFS after curative surgery of hilar cholangiocarcinoma and we also analyzed the factors associated with tumor free margin, so it is essential to retain the part “As was shown in table 3, OS was significantly longer in patients with no lymph node metastasis ($P<0.001$), well histological.... ”. And if it seems improper, I would revise it again. Thank you so much for your experiential advice.

(Q4) Intra-operative palliation was superior to nonsurgical palliation in patients who lost the chance of undergoing major resection”. However this includes a bias since patient with better performance status could underwent surgery and they were expected to have better survival. This may be valid also for caudate lobectomy.

Answer: Thank you very much for this comment. We are terrible sorry for our little experience in preparing manuscript. In our study, palliative surgery include intra-operative palliation and nonsurgical palliation, intra-operative palliation means intraoperative T tube drainage and nonsurgical palliation means ERCP or PTCD, the palliative surgery was conducted in patients who lost the chance of undergoing curative intent surgery. For curative surgery, caudate lobectomy was regularly moved

in our study, excepted for some earlier cases of type I papillary carcinoma or in the first several years of our study. And we have carefully evaluated the patients when we choose the surgical procedures, patients with any of the following were considered to be unresectable: poor conditions, Child-Pugh C, advanced biliary invasion that excludes complete tumor resection, encasement of major vessel structures that eliminate vascular reconstruction, lymph nodes metastases beyond the hepatoduodenal ligament, metastatic disease (lung and peritoneum metastases).

Indeed, as you have mentioned, the resectability rate may vary from one surgeon to another, for some specific cases, some surgeons may underwent curative surgery while in other surgeons, it seems difficult to operate curative surgery, this include the removal of the caudate lobe and portal vein resection, and the caudate lobe and portal vein resection can improve the long-term survival rate. But not all surgeons can finish this surgical procedure, and this was one of the difficult points of hilar cholangiocarcinoma. As was said in our current studies, in our hospital, caudate lobe resection was not conducted in the earlier cases of hilar cholangiocarcinoma patients. Because based on the technical and conditions of that time, it seems to be difficult to undergo caudate lobe resection for all patients. The resectability rate at that time seems to be less than 10%, while the resectability rate at our current time seems to be 30% - 40%. In recent years, with the development of medical science and the multi-disciplinary cooperation, and with the discussion of the whole department and designated medical practitioner, the resectability rate and R0 resection improved significantly. And this was comparable to the resectability rate of the whole nation and the whole world.

In our current study, we reported intra-operative palliation was superior to nonsurgical palliation in patients who lost the chance of undergoing curative resection, the reason may be lies in the following factors: intraoperative palliation could directly relieve the bile duct obstruction by completely opening bile duct at the hilar bifurcation as much as possible, facilitating whole biliary decompression and finally enhancing liver function and survival outcomes, while the PTCD does not show this kind of advantage. And in order to reduce bias, in the discussion part, we add “However, further studies with more number of cases are needed in future to testify the reasonability of whether surgical palliation is superior to nonsurgical palliation. In the long run, compared with the curative surgery, we convincingly believe that curative surgery is the best way in prolonging the survival outcome.” in the page 12, line 3. In the conclusion part, we deleted the sentence “Intraoperative palliation is superior to nonsurgical palliation in lowering the probability of bile duct obstruction and completely opening bile duct, thus liver function in this respect can be improved and better survival outcomes can be expected to some extent. Therefore, as for those patients who lost the chance of undergoing major resection, surgical palliation is recommended.” After all, it was not the main purpose of our study. My dear reviewer, if you think there also exist some mistakes and improper parts, I would revise it again. Thank you so much for your experiential advice.

Reviewer #2 (02462252):

This is a good overview of an interesting and relatively common cancer. Will be of interest to the readership.

Answer: First of all, thank you so much for reviewing our manuscript and giving us a high evaluation, and we will try our best to make a further research in this respect.

Reviewer #3 (00722050):

The authors present one of the largest series of HCCA. The presentation of data is clear and scientifically sound. I would suggest some aspects that may be targeted by the authors.

(Q1) There is quite a lot of misspellings and grammar mistakes. Since the manuscript is very nice and brings remarkable outcome data, it needs a revision by a native English speaker, who should work in a biomedical field.

Answer: Thank you so much for reviewing our manuscript, according to your experiential advice, we have invited a native English speaker to examine the grammatical, spelling mistakes, and then polish it. To conserve the layout of printed sheet, I deleted some repeated contents, such as results in the discussion section, and condense some paragraph into one paragraph. Also, I deleted some minor important contents. If this kind of revision is inappropriate, please put up your precious and professional suggestion, and I would revise it again. Thank you so much!

(Q2) If 814 patients from 1990 through 2014 have been analyzed, a figure showing some epidemiology is important.

Answer: Thank you very much for this comment. We have depicted patient numbers, median patient ages, genders, present manifestations, the tumor markers, the liver functions, the hospital stay, the preoperative biliary drainage, the surgical procedures et.al in table 1 and table 2, so I am wondering is it ok for the epidemiology information you mentioned in the reviewing comments. If you think there also exist some mistakes and improper parts, I would revise it again. Thank you so much for your experiential advice.

(Q3) The etiology should be also chartered with a pie or a histogram. In particular, I am interested to know if ductal plate malformation lesions have been found or not. This should put as statement (please read and cite numerous publications of Sergi-C with liver lesions including ductal plate malformation, among others American Journal of Pathology, 2000)

Answer: Thank you very much for this comment. There are some established risk factors for hilar cholangiocarcinoma such as the liver fluke infestation, the oriental

cholangiohepatitis, the biliary duct cysts, the primary sclerosing cholangitis, the hepatolithiasis, and toxins exposure. Moreover, different patterns of lifestyle such as the tobacco or alcohol consumptions, the regional factors, the variations in genetic susceptibility may also play a role in affecting pathogenesis of hilar cholangiocarcinoma. However, its real cause is unknown and the majority of patients present without a known risk factor. So, it was difficult to provide the exact etiology histogram. And we have already added the depiction of etiology in the introduction part in page 5, line 8, and we added “A variety of established risk factors are reported to increase the odds of hilar cholangiocarcinomas, which include the primary sclerosing cholangitis, the biliary duct cysts, the oriental cholangiohepatitis, the hepatolithiasis, the biliary parasitic disease and the toxins exposure, the specific etiology is still unclear.” We are wondering if this is ok and if it seems improper or it may induce ambiguity, I would revise it again.

The ductal plate malformation is a developmental anomaly in which the fetal ductal plate persists after birth, which includes choledochal cyst, Caroli’s disease and Caroli’s syndrome, adult autosomal dominant polycystic liver disease, and biliary hamartoma. And there are also some cases reporting about intrahepatic cholangiocarcinoma with ductal plate malformation. In our studies, patients with ductal plate malformations have not been found. However, in the future, we will collect more number of patient cases and cooperate with other institution to discuss the ductal plate malformations in our next series. And if it seems improper or it may induce ambiguity, I would revise it again. Thank you so much for your experiential advice.

(Q4) A schema of the Bismuth-Corlette classification should be added.

Answer: Thank you very much for this comment. Bismuth-Corlette classification was a well-established classification system for hilar cholangiocarcinoma, and it was divided into 5 types; Type I affects the common hepatic duct, distal to the confluence of the left and right hepatic ducts. Type II affects the confluence of the right and left hepatic ducts. Type IIIa affects the right hepatic duct in addition to the confluence. Type IIIb affects the left hepatic duct in addition to the confluence. Type IV refers to cholangiocarcinoma involving the confluence and both right and left hepatic ducts or to multifocal cholangiocarcinoma. And we have already add the classification system in our current studies in the introduction part, we added: “On the basis of the Bismuth classification, hilar cholangiocarcinoma can be divided into 4 types: type I represents for tumors affecting the common hepatic duct, type II represents for tumors affecting the hilus, type III A/B represents for tumors invading the right or left hepatic duct, type IV with tumors infiltration of both right and left hepatic ducts and the sub-segments” in page 5, line 4 And if it seems improper or it may induce ambiguity, I would revise it again. Thank you so much for your experiential advice.

(Q5) More data should be discussed with regard to the caudate lobectomy.

Answer: Thank you very much for this comment. We are terrible sorry for our little experience in preparing manuscript. We have added some elucidation in my revised manuscript. As we know, caudate lobectomy was also proved as an important factor in many previous studies. In our current study, caudate lobe was routinely removed, and we analyzed the prognostic effect of caudate lobectomy on the postoperative OS and DFS, and we also analyzed the factors that could affect the postoperative complications, including the caudate lobectomy. Finally, we studied factors correlated with R0 resection. In the final analysis, the OS and DFS were found to be significantly longer in patients with caudate lobectomy as compared with those without caudate lobectomy in the univariate analysis (median OS 35.7 : 21.4 months, median DSF 21.3 : 15.0 months; $P=0.04$ and <0.001 respectively), caudate lobectomy was approaching statistical significance as a positive prognostic factor for OS in multivariate analysis (HR=1.257, 95%CI 0.981-1.612, $P=0.071$). But it was not associated with DFS in the multivariate analysis. Moreover, the postoperative complication was not correlated with caudate lobectomy. Furthermore, it was also an independent factor for tumor-free margin in our current series (OR=10.236, 95%CI 4.738-22.116, $P<0.001$). Thus, we firmly believe that this procedure should be considered as a part of the standard surgical resection. In the discussion part, we added “and it was not associated with postoperative complications” in page 14, line 11. And if it seems improper or it may induce ambiguity, I would revise it again. Thank you so much for your experiential advice.

(Q6) Was identified any biliary intraepithelial neoplasia in your 814 patients? Thank you

Answer: Thank you very much for this comment. Indeed, there really existed biliary intraepithelial neoplasia in our current case, with lesser number of cases. And we are intended to make a further analysis in this regard. We will present further results in this respect in our future analysis. And if there is any question concerning this side, please, do not hesitate to contact me.

Reviewer #4 (03317310):

This paper reports the large experience of the Chendu Hospital, China, 814 patients with cholangiocarcinoma, 381 operated in a curative intent. From this extensive experience the authors performed a statistical analysis to estimate prognostic factors of outcome.

(Q1) Was non surgical treatment as chemotherapy or irradiation proposed to some patients; in a palliative setting or as adjuvant treatment? Any cases of cirrhosis associated or responsible?

Answer: Thank you very much for this comment. As a matter of fact, radiation did not

improve survival, even worse, it may result in hepatic decompensation. At present, there is little evidence supporting the routine use of chemotherapy in patients diagnosed as hilar cholangiocarcinoma. And chemotherapy was often used in those after liver transplantation, and it was reported patients underwent liver transplantation combined with chemotherapy could achieve better survival outcome. However, at first, we excluded those who underwent liver transplantation in our center, and for the rest of patients underwent curative or palliative surgery, the chemotherapy was not regularly used. And in some specific cases, the chemotherapy and radiation was conducted, however, the results was dissatisfactory, the cases were also relatively less, thus, it was not reported in our present study. Many patients in our center gave up the chemotherapy and radiation when they were being told the results was not that good. We will accumulate and collect more medical records in future about the patients undergoing postoperative radiotherapy and chemotherapy, and will discuss and explore the value of chemotherapy and radiation in treating hilar cholangiocarcinoma with scholars home and abroad.

As for the cirrhosis, in our study, cirrhosis was also analyzed as a potential prognostic factor in survival analysis, but it was not associated with survival. And if it seems improper or it may induce ambiguity, I would revise it again. Thank you so much for your experiential advice.

(Q2) P 8: survival analysis: I do not understand how patients who had non surgical palliation had a median OS of 2.6 months while they have a median DFS of 5.5 months.

Answer: Thank you very much for this comment. We are terrible sorry for our little experience in preparing manuscript. In the paragraph, we wrote “As for patients who did not take any surgical treatment, the median OS and the 1-, 3-year survival rate was 2.6 months and 1% and 0%, respectively (Figure 1, log-rank test, $P < 0.001$). Furthermore, we compared the survival rate of those underwent surgical palliation and nonsurgical palliation, the former had a median survival time and 6-month survival rate of 7.4 months and 27% respectively, while the latter had a median survival time of 5.5 months and 6-month survival rate of 9% respectively ($p < 0.001$).”

In fact, in our analysis, patients were divided into 3 groups: patients who underwent curative surgery, those who only take palliative surgery (include Intra-operative palliation and nonsurgical palliation, intra-operative palliation means intraoperative T tube drainage and nonsurgical palliation means ERCP or PTCD) and those who did not take any surgery. At first, we wrote the median OS for patients who did not take any surgical treatment was 2.6 months, here, the patient referred to the one who did not take curative surgery or palliative surgery. Then we wrote nonsurgical palliation (ERCP or PTCD) had a median survival of 5.5 months. The reason why we list those who did not take any treatment in our manuscript was to compare the survival outcome among the curative group, the palliative group, and

those who did not take any treatment, concluding that better survival was expected in the curative group. And patients in the palliative group also had a relative better survival than those who did not take any treatment. These terminologies were used in accordance with some previous studies. And if it seems improper or it may induce ambiguity, I would revise it again. Thank you so much for your experiential advice.

(Q3) P11: It is frequently said but difficult to write that R2 resection was better than no resection ... in my mind it is because tumor size, vascular invasion, etc ... were different and all these criteria are associated with survival. Then I propose to remove the last sentence of the conclusion, as in 2015 we have “some efficient” systemic or radiotherapeutic options.

Answer: Thank you very much for this comment, which is great helpful to consummate our research. Indeed, previous studies have documented a relative better survival outcome in patients with R1 and R2 resection when compared with those who did not undergo resection. The R1 and R2 resection could roughly remove tumor and the root of obstructive jaundice and adequately open biliary tract and then the liver function could be improved and relatively better survival outcomes can be expected to some extent. We admitted that patients selected for resection definitely have better preoperative conditions. Patients with any of the following were considered to be unresectable: poor conditions, Child-Pugh C, advanced biliary invasion that excludes complete tumor resection, encasement of major vessel structures that eliminate vascular reconstruction, lymph nodes metastases beyond the hepatoduodenal ligament, metastatic disease (lung and peritoneum metastases).

Now vascular invasion was not a contradiction for curative resection any more. For patients who have vascular invasion, the vascular resection and reconstruction may be adopted and this was reported by various studies. Tumor size was also an important factor in our current study; it could affect the overall survival and it could also affect the tumor-free margin, thus, the patients with smaller tumor size (< 3 cm) had a higher incidence of obtaining tumor free margin, but it was also not a contradiction for undergoing curative resection. And there were also other factors that may induce a bias when we took these two factors into consideration and compared the survival outcome between those who underwent R2 resection and those who did not take any surgical treatment, and we think your advice here was very helpful. Thank you so much for your experiential advice and we have made some relative changes in the conclusion of our revision. We have already deleted the last sentence in the conclusion part, and if it seems improper or it may induce ambiguity, I would revise it again. Thank you so much for your experiential advice.

(Q4) There are too many figures; 4 – 5 will be enough.

Answer: Thank you very much for this comment. We also think there are too many figures in the text, and we are confused by this all the time, on the one hand, if we remove some figures in the text, we are wondering that our manuscript will be less persuasive, and if we retain all the figures, it seems to many. So in my revised manuscript, we deleted some minor important figures.

Since the main aim of our current study was to analyze factors associated with survival, we also examined the prognostic factors associated with tumor free margin. The tumor differentiation and lymph node metastasis was well defined prognostic factors correlated with survival, herein, we deleted the overall survival and disease free survival of patients who underwent curative surgery for hilar cholangiocarcinoma stratified by tumor differentiation and lymph node metastasis, and we retain the figure of tumor size with overall survival, for it can prove the rationality of the T stage of DeOliveira staging system. And we retain the figures of tumor margin with OS and DFS in our manuscript, for in the further analysis, we examined factors associated with tumor free margin. We also retain the figures of vascular invasion with OS and DFS, for it was associated with tumor free margin in the further analysis.

My dear reviewer, I do not know this answer is proper or not. And if it seems improper or it may induce ambiguity, I would revise it again. Thank you so much for your experiential advice.

(Q5) This extraordinary experience ranges from 1990 to 2014, can they know if these results are also depending on their experience / earlier diagnosis ?

Answer: Thank you very much for this comment. Our study was a single center experience containing 814 patients with hilar cholangiocarcinoma, ranging from 1990 to 2014, and was one of the largest cases dealing with the survival outcome of hilar cholangiocarcinoma. We have a large database, and patients diagnosed as hilar cholangiocarcinoma would be admitted into the database. Hilar cholangiocarcinoma is characterized by painless obstructive jaundice, thus, many patients remain asymptomatic until late and the imaging findings of smaller tumors are usually easily overlooked. And based on the national situation of our country, most of the patients were present late with the classical symptoms and the tumors tend to be locally advanced, which was associated with a delayed diagnosis and treatment for the eastern hilar cholangiocarcinoma cases. So, we believe that our result was not associated with earlier diagnosis.

But with the advance of medical science and imaging technology, we believe earlier diagnosis is possible in the future. And with the development of our country, the life quality of people has improved, so many patients will come to the hospital earlier when they feel discomfort, this may lead to the earlier diagnosis.

Indeed, this was just a collection of our single center experience; we are also

working with other units and merging the databases, to obtain a better result of a much larger sample of multi-center research and provide a more valuable article in this field. And if this answer seems improper or it may induce ambiguity, I would revise it again. Thank you so much for your experiential advice.

(Q6) Tumor size is associated with OS and not with DFS: is it related to post-op mortality / severe morbidity alone?

Answer: Thank you very much for this comment. Tumor size is an important prognostic factor, as it can directly affect the vascular system and resectability rate. Larger tumor size being more likely to invade the portal vein, the hepatic artery and bile duct system, thus resulting in wider scope of liver resection, with longer peri-operative time and higher amount of blood loss. Many previous studies have reported tumor size was associated with survival.

In our current study, tumor size was also a significant prognostic factor, it could affect the overall survival and it could also affect the tumor-free margin, thus, the patients with smaller tumor size (< 3 cm) had a higher incidence of obtaining tumor free margin, while it was not associated with the disease-free survival in our study, and we also analyzed factors associated with postoperative complications after curative surgical resection, only to find that tumor size was not associated with postoperative complications, and because of the most common cause for operative mortality was multiple organ failure and patients died at the perioperative period were relative less with only 10 cases for curative resection, so in order not to induce a bias, we did not analyze whether tumor size was correlated with post-op mortality. And if it still seems improper or it may induce ambiguity, I would revise it again. Thank you so much for your experiential advice.

(Q7) Minor: p8: well differentiation p8: smaller tumor size: give the cut off value Table 4: to redraw

Answer: Thank you very much for this comment. In fact, hilar cholangiocarcinoma has three histological differentiation type, which contains the well-differentiated, the moderately-differentiated and the poorly differentiated, and as was reported by many previous studies, patients with well tumor differentiation had better survival outcome while those with poor tumor differentiation had poor survival outcome. So, I was wondering whether the well differentiation can be retained. And in our study, tumor size was divided by the 3 cm cut-off, and we have already changed the p8: smaller tumor size into tumor size ≤ 3 cm. we have already redesigned the table 4. And if it still seems improper or it may induce ambiguity, I would revise it again. Thank you so much for your experiential advice.

Reviewer #5 (03317310):

The major objective of this study is to evaluate the prognostic factors of hilar

cholangiocarcinoma in a large series of patients in a single institution. The authors reviewed 814 patients who have been divided into 3 groups according to their various treatment. Potential factors associated with overall survival (OS) and disease free survival (DFS) were evaluated by univariate and multivariate analysis. The author found that tumor margin, tumor differentiation, vascular invasion and lymph node status were independent factors for OS and DFS. The data in this paper looks solid, and English is fairly ok.

(Q1) The major concern for the paper is the innovation as most of the results here have been reported previously. Therefore, the author needs to emphasize their innovation and its potential contribution for clinical application in the discussion part and convince the reviewers.

Answer: I am very grateful to your comments for the manuscript. Hilar cholangiocarcinoma remains among the most difficult management problems faced by surgeons. Many authorities have reported various prognostic factors of HCCA; however, due to the difference in study methods and small patient numbers in other studies, it might cause potential biases or even contradictory outcomes. Furthermore, some large cases of multi-center reports might induce biases due to the heterogeneity of clinical methods and surgical strategies. Thus a large number of HCCA cases of single center experience are urgently needed to standardize the prognostic factors and to supply better guidance and treatment for HCCA, and we think our current study was essential and useful.

In our current study, we analyzed factors with overall survival and disease free survival after curative resection of hilar cholangiocarcinoma in an institution of China; and then we evaluated factors that could contribute to the obtaining of R0 resection so as to help future surgical decision making.

In our current study, tumor size was an important prognostic factor; tumor size > 3 cm was associated with poor overall survival outcome and patients with tumor size > 3 cm was less likely to have R0 resection margins. But tumor size was not associated with disease free survival. No other previous studies have defined this kind of relevance as clear as us, and our present study was in accordance with the staging system proposed by DeOliveira et al. in the DeOliveira staging system, the 3 cm cut-off of tumor size was defined as T3, however, the competence of the T stage in the DeOliveira staging system in predicting the nature of this tumor or the postoperative survival outcome could not be verified currently.^[1] So our results here proved that the 3 cm of tumor size cut-off was an important prognostic factor and the T3 stage was reasonable in this regards.

In the previous study, there was also little evidence about factors associated with R0 resection, and the results differ from one institution to another. Since R0 resection conferred to an admirably better survival outcome, which was reported in most

published articles and reconfirmed in our current studies. Thus, we analyzed factors correlated with R0 resection, and in the multivariate analysis, hepatectomy, tumor diameter, AJCC T stage, caudate lobectomy and vascular invasion were proved to be independently associated with tumor-free margin and no previous studies have defined this kind of relevance as clear as us.

Hepatectomy was a significant factor for the treatment of hilar cholangiocarcinoma, and in contrast to most previous studies, hepatectomy could directly affect the survival outcome of hilar cholangiocarcinoma, we identified hepatectomy was an indirect prognostic factor associated with survival, as patients with hepatectomy had a higher incidence of obtaining tumor-free margin, and no other studies have defined this kind of relevance as clear as us.

Caudate lobectomy was also proved as an important factor in many previous studies, in our current study, caudate lobectomy was approaching statistical significance as a positive prognostic factor for OS in multivariate analysis (HR=1.257, 95%CI 0.981-1.612, P=0.071). Furthermore, it was also an independent factor for tumor-free margin in our current series (OR=10.236, 95%CI 4.738-22.116, P<0.001). Thus, we firmly believe that this procedure should be considered as a part of the standard surgical resection.

Based on the above factors, we believed that our current study was novel and it would undoubtedly play a role in future preoperative decision making and firmly guide the treatment and predict the prognosis after surgery. My dear reviewer, I do not know this answer is proper or not. And if it still seems improper or it may induce ambiguity, I would revise it again. Thank you so much for your experiential advice.