Response Letter

Dear editors and reviewers,

Thank you so much for the opportunity for revision. We have read the comments of you and the reviewers carefully and we have changed the manuscript accordingly. In this letter, we have responded to each below, on a point-by-point basis. In the revised manuscript, most changes were highlighted.

Reviewer #1 (03727922):

Interesting manuscript entitled "Focal intrahepatic strictures: diagnosis-treatment experience and a proposal classification", however I suggest some structural modifications to improve your manuscript. I believe that you have to decide if the main objective is to report your cases, review the literature or establish a "new" classification. The topic caught my attention and to me needs a better description of the methodology on the review carried out. And that will certainly give more importance to your manuscript. I suggest to perform a better description of the methodology carried out using PRISMA statment and thus continue with the results. Of course, you can make a general table (or results) with the results and place your results and compare with the literature. Finally, within the main findings, I believe that in the discussion you could propose a "new" classification as a benefit for medical practice.

Response: Thank you very much for your important suggestions. According to your instruction, we have modified the title our manuscript as "Focal intrahepatic strictures: a proposal classification based on diagnosis-treatment experience and systemic review." (Please see the new "title", page 1.)

Then, we have tried to introduced the "PRISMA statement" into our manuscript but we found that the type of the included articles might not suit for using the above statement due to the following two reasons: (1) We have tried searching the papers concerning the comparing the advantages and disadvantages between various diagnostic or treatment methods. However, because of the low incidence rate of FIHS, there was very few published clinical trials or comparative studies concerning these issues. Some studies like Tokala, Ajay et al. "Comparative MRI analysis of morphologic patterns of bile duct disease in IgG4-related systemic disease versus primary sclerosing cholangitis." AJR. American journal of roentgenology vol. 202,3 (2014): 536-543. doi:10.2214/AJR.12.10360, reported cases of both FIHS and extrahepatic biliary strictures. Therefore, it might be difficult to extract accurate data from these studies. As also noted in our manuscript, aspiration, brush cytology and biopsy are the three main methods for obtaining preoperative pathology for biliary malignancy. Unfortunately, almost all the data of their sensitivity, specificity,

positive predictive value (PPV), and negative predictive value (NPV) were acquired based on their applications in diagnosing strictures associated with CBD or near porta hepatis so that there has been little evidence supporting their efficacy for diagnosing FIHS. (2) Our study did not focus on the comparing different treatment or diagnostic methods for handling FIHS but tried to outline its etiology, diagnosis and treatment experiences. Of course, we are still so appreciated for your suggestion and because there are important lessons to be drawn from the "PRISMA statement". As so, we modified the part of "Literature Review" and added the "Inclusion and Exclusion Criteria" for selecting the papers. (Please see the part of "MATERIALS AND METHODS", "Literature Review", page 7, Line 90-95.) and Figure Suppl 1: Chart flow of study selection (next page).

Besides, according to your instruction, we added the statement of "Ethical Issues" which was also critical for clinical research as follows: The study was performed in accordance with the declaration of Helsinki. Ethical approval for the present study was granted by XinHua Hospital affiliated to Shanghai JiaoTong University, School of Medicine (Shanghai, China) . The study was strictly in accordance with the Declaration of Helsinki and International Ethical Guidelines for Health-related Research Involving Humans. All the included patients signed a informed consent form. A multidisciplinary team made up of hepatobiliary surgeons, radiologists, oncologists, gastroenterologists and pathologists selected candidates for the treatment together. (Please see the part of "MATERIALS AND METHODS", "Ethical issues", page 6-7, Line 55-63.)

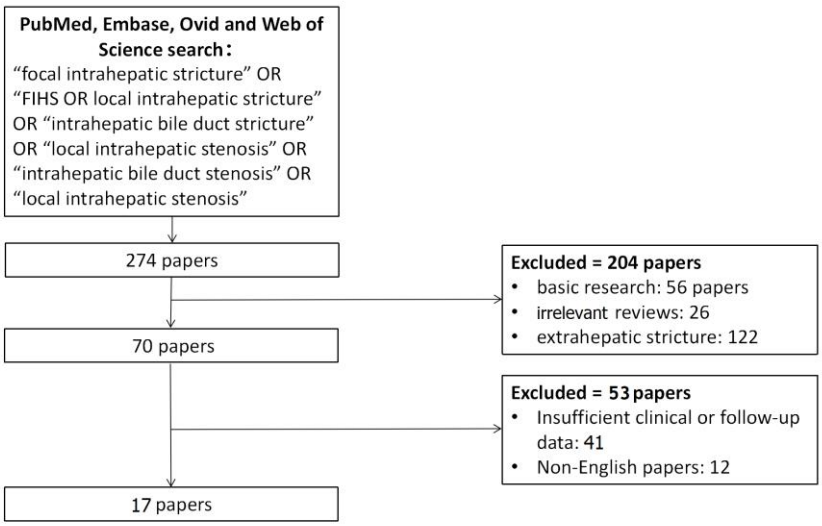

Figure Suppl 1. Chart flow of study selection.

Reviewer #2 (01560036):

According to your paper, FIHS is complication of the main disease

(cancer, bile stones). I am not shure that FIHS should be separate as a special disease. The treatment is directed to the main disease with simultaneous remowing of FIHS. To my mind, special classification for FIHS treatment is unneccessary.

Response: Thank you very much for your comment. As you pointed out, we also agree that FIHS might not be separate as a special disease and the treatment is directed to the main disease with simultaneous removing FIHS. However, because of the incidence rate of FIHS is extremely low and it is easily misdiagnosed or missed diagnosed, we proposed a classification as follows:

Type I: FIHS located within one segment of the liver; type II: FIHS located at the confluence of the bile ducts of one segment or two adjacent segments; type III: FIHS connected to the left or right hepatic duct; and type IV: multiple FIHS located in both lobes of the liver. The following two reasons for the above proposed classification are:

Firstly, qualitative and localization diagnosis of FIHS are difficult points. to date, routine imaging examinations such as ultrasound, CT, MRI and PET do not have sufficient sensitivity and specificity required for diagnosing FIHS. Therefore, combined applications of endoscopy with pathology might has better application prospect in the future. Considering the distance between the location of FIHS and the edge of the liver, PTCD might has better application prospect for for type I or II patients whose FIHS are located close to the surface of the liver or the abdominal wall to achieve drainage or pathological diagnosis. Correspondingly, ERCP might be more suitable for FIHS connected to the LHD and RHD (type III). Ultrasound or CT-guided puncture biopsy is the most commonly used method for the qualitative diagnosis of type IV FIHS. For the surgical approaches, partial hepatectomy, segmentectomy and hemihepatectomy are applicable for type I, II and III patients, respectively. For type IV patients, surgeons should first exclude diagnoses of immune-mediated hepatobiliary diseases.

Then, the treatment for FIHS, especially the extent of liver resection and its effect on post-surgery residual hepatic volume and function might be closly correlated with the location of FIHS. Therefore, we believe that set up a classification for FIHS is still necessary.

Reviewer #3 (03017551):

First - the proposed a new classification system to guide the diagnosis and treatment of FIHS (type I -IV) Second - the conclusions appropriately summarize the data that in this study Third - the very interesting conclusions.

Response: Thank you very much for your good comments to our manuscript.