

Response to Reviewer #1 :

Thank you very much for your questions. We would like to response to your questions as the following:

[Question 1].

Reviewer #1:

1. There are limited population-based data available for investigations into epidemiologic characteristics of ICC in some particular area, while the author have a national cancer registry database system that can be used and it is good for evaluating the secular trends of ICC in Taiwan.

Response:

Thank you for your appreciation.

[Question 2].

2. The ICC has several risk factors, such as aging, smoking, obesity, diabetes mellitus and so on. In this study, the author evaluated secular trends of ICC according to age and sex in Taiwan. The assessment of other independent and/or interactive effects are suggested, and future prospective evaluations are needed to explore potential risk factors of ICC.

Response:

It was mentioned in the revised manuscript (page 13, line 4-8).

Ultimately, although our study found that there are various risks associated with ICC, including sex, age, DM, HBV and/or HCV infection, obesity, nutritional factors, and smoking, the results need to be validated in larger cohorts, exploring the risk of ICC development in a high incidence area in particular.

Reviewer #2:

[Question 1].

I would like to thank the Editor and the Authors for the opportunity to review this paper. It is an interesting paper and well reported. The Authors report in details the epidemiology of ICCA. However, at least in the discussion, I would like to suggest to add information regarding the nutritional aspect of increasing case of ICCA because it is a well known condition that impact in postoperative complications and survival in patients with

Cholangiocarcinoma as reported in recently papers like "Ardito F, Coppola A, Rinninella E, Razionale F, Pulcini G, Carano D, Cintoni M, Mele MC, Barbaro B, Giuliani F. Preoperative Assessment of Skeletal Muscle Mass and Muscle Quality Using Computed Tomography: Incidence of Sarcopenia in Patients with Intrahepatic Cholangiocarcinoma Selected for Liver Resection. J Clin Med. 2022 Mar 10;11(6):1530. doi: 10.3390/jcm11061530. PMID: 35329856; PMCID: PMC8956038."

Response:

Surgery is the only curative treatment for ICC<sup>[4]</sup>. A previous study found the incidence of sarcopenia among ICC patients following receipt of liver resection to be 50%. Preoperative nutritional evaluation is important for ICC<sup>[41]</sup>. In addition, nutritional factors may affect the disease incidence. Indeed, a population-based cohort study found that regular use of oil supplement lowered the risk of total liver cancer to 44% (95%CI: 25%-59%) and risk of ICC to 40% (95%CI: 7%-61%)<sup>[42]</sup>. A meta-analysis suggested that vegetable and fruit consumption may reduce the risk of ICC; specifically, the reported ORs of mixed vegetables, mixed fruits, and combined fruits and vegetables were 0.61 (95%CI: 0.50-0.75), 0.79 (95%CI: 0.65-0.96), and 0.68 (95%CI: 0.57-0.80), respectively<sup>[43]</sup>. A multi-center study determined that high dietary fiber intake could be associated with a lower risk of intrahepatic bile duct cancer<sup>[44]</sup>. Finally, an animal model-based study in Taiwan provided further evidence of a relationship between ICC and nutrition; vitamin D supplementation lead to significant suppression of ICC initiation and progression in the rat model *via* regulation of gene expression (*e.g.*, of lipocalin 2)<sup>[45]</sup>.

Add reference:

41 **Ardito F**, Coppola A, Rinninella E, Razionale F, Pulcini G, Carano D, Cintoni M, Mele MC, Barbaro B, Giuliani F. Preoperative Assessment of Skeletal Muscle Mass and Muscle Quality Using Computed Tomography: Incidence of Sarcopenia in Patients with Intrahepatic Cholangiocarcinoma Selected for Liver Resection. J Clin Med 2022 Mar;11:1530 [PMID: 35329856 DOI: 10.3390/jcm11061530]

42 **Jiang W**, Li FR, Yang HH, Chen GC, Hua YF. Relationship Between Fish Oil Use and Incidence of Primary Liver Cancer: Findings From a Population-Based Prospective Cohort Study. Front Nutr 2021;8:771984 [PMID:

35036409 DOI: 10.3389/fnut.2021.771984]

43 **Songserm N**, Woradet S, Charoenbut P. Fruit and Vegetables Consumption: A Pointer for Cholangiocarcinoma Prevention in Northeast Thailand, the Highest Incidence Area in the World. *Nutr Cancer* 2016;68:1289-1294 [PMID: 27682423 DOI: 10.1080/01635581.2016.1225101. Epub 2016 Sep 28]

44 **Fedirko V**, Lukanova A, Bamia C, Trichopolou A, Trepo E, Nöthlings U, Schlesinger S, Aleksandrova K, Boffetta P, Tjønneland A, Johnsen NF, Overvad K, Fagherazzi G, Racine A, Boutron-Ruault MC, Grote V, Kaaks R, Boeing H, Naska A, Adarakis G, Valanou E, Palli D, Sieri S, Tumino R, Vineis P, Panico S, Bueno-de-Mesquita HBA, Siersema PD, Peeters PH, Weiderpass E, Skeie G, Engeset D, Quirós JR, Zamora-Ros R, Sánchez MJ, Amiano P, Huerta JM, Barricarte A, Johansen D, Lindkvist B, Sund M, Werner M, Crowe F, Khaw KT, Ferrari P, Romieu I, Chuang SC, Riboli E, Jenab M. Glycemic index, glycemic load, dietary carbohydrate, and dietary fiber intake and risk of liver and biliary tract cancers in Western Europeans. *Ann Oncol* 2013;24:543-553 [PMID: 23123507 DOI: 10.1093/annonc/mds434. Epub 2012 Nov 2]

45 **Chiang KC**, Yeh CN, Lin KJ, Su LJ, Yen TC, Pang JH, Kittaka A, Sun CC, Chen MF, Jan YY, Chen TC, Juang HH, Yeh TS. Chemopreventive and chemotherapeutic effect of dietary supplementation of vitamin D on cholangiocarcinoma in a Chemical-Induced animal model. *Oncotarget* 2014 Jun 15;5(11):3849-3861 [PMID: 24939880 DOI: 10.18632/oncotarget.2000]

Delete the duplicate reference:

15 **Saha SK**, Zhu AX, Fuchs CS, Brooks GA. Forty-Year Trends in Cholangiocarcinoma Incidence in the U.S.: Intrahepatic Disease on the Rise. *Oncologist*. 2016;21:594-9 [PMID: 27000463 DOI: 10.1634/theoncologist.2015-0446]

40 **Mosadeghi S**, Liu B, Bhuket T, Wong RJ. Sex-specific and race/ethnicity-specific disparities in cholangiocarcinoma incidence and prevalence in the USA: An updated analysis of the 2000-2011 Surveillance, Epidemiology and End Results registry. *Hepatol Res*. 2016;46:669-77 [PMID: 26508039 DOI: 10.1111/hepr.12605]