

Point-by-point responses:

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: This manuscript aimed at investigating the association between the burden of Primary liver cancer (PLC) and socioeconomic development status. Cancer mortality and incidence rates were obtained from GBD 2019 and the data were stratified by country and territory, sex, and level of socio-demographic index (SDI). The association between attributable etiology of PLC and socioeconomic development status, represented by the SDI, was described. Attributable etiology of PLC included hepatitis B, hepatitis C, alcohol use, and nonalcoholic steatohepatitis. this study revealed that In terms of incidence rate, the first leading underlying cause of PLC was identified as hepatitis B, followed by hepatitis C, alcohol use, and nonalcoholic steatohepatitis. Stratified using SDI, the incidence rate of PLC was the highest for high and middle SDI locations. Further, the leading attributable etiology of PLC was found to be hepatitis B for middle, high middle SDI locations whereas they were hepatitis C and nonalcoholic steatohepatitis for high SDI locations. The study raised the hypothesis that socioeconomic development status affects the attributable etiology of PLC. The data of GBD 2019 are valuable for policymakers in implementing cost-effective interventions for PLC. However according to the limitations mentioned by the authors, the study carried out depending to global data usually lacks accuracy. There is a possibility of the underestimation of PLC burden in low middle and low SDI locations because of inadequate cancer screening and lack of registration. So, similar studies may raise hypothesis, but did not give an evidence based conclusion. This study needs language revision.

Response to Reviewer #1: Thank you very much for your keen advice! We have added additional information regarding this topic in the Limitations subsection of the Discussion section on page 24-25, lines 470-475.

We will seek language polishing before we submit the amended manuscript.

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors: The aims of the current study was to identify the effect of socioeconomic development status on the attributable etiologies of PLC from a global perspective. Cancer mortality and incidence rates were obtained from GBD 2019 and the data were stratified by country and territory, sex, and level of socio-demographic index (SDI). The association between attributable etiology of PLC and socioeconomic development status, represented by the SDI, was described. Attributable etiology of PLC included hepatitis B, hepatitis C, alcohol use, and nonalcoholic steatohepatitis. The association between attributable etiology of PLC and SDI was further stratified by sex and geographical location. In terms of incidence rate, the first leading underlying cause of PLC was identified as hepatitis B, followed by hepatitis C, alcohol use, and nonalcoholic steatohepatitis. Association was identified between socioeconomic development status and burden of PLC. Leading attributable etiology of PLC was hepatitis B for middle, high-middle sociodemographic index (SDI) locations. Leading attributable etiology of PLC was hepatitis C and nonalcoholic steatohepatitis for high SDI locations. Between 1990 and 2019, PLC caused by hepatitis B and hepatitis C showed a decreasing trend in the death rate. Countries that possessed the highest-burden of the PLC incidence rate also had the highest burden of the PLC death rate. The most probable explanation of the findings is the underestimation of PLC burden in low middle and low SDI locations because of inadequate cancer screening. This issue needs to be addressed in more detail and be supported by relevant literature. Otherwise the study is interesting, it contains a large amount of data, but should not pass erroneously the message that high SDI location is by itself an independent risk factor for liver cancer. Socioeconomic status (SES) is one of the many factors influencing a person's alcohol use and related outcomes. Findings have indicated that people with higher SES may consume similar or greater amounts of alcohol compared with people with lower SES, although the latter group seems to bear a disproportionate burden of negative alcohol-related consequences. Also low socioeconomic status has been associated with an increased risk of HCV infection and with poor prognosis in HCV infected patients. Also, Hepatitis B transmission is also associated with low socioeconomic

status. I think that these issues should also be addressed as the results of this study differ from the literature. In conclusion, I think that the study is interesting and can be concerned for publication in the journal after minor revisions.

Response to Reviewer #2: Thank you for your helpful advice! We added content to the manuscript regarding the underestimation of PLC in low- and middle-income countries in the Limitations subsection of the Discussion section on page 24-25, lines 470-475.

Exactly as you pointed out, there is an increased risk of HBV and HCV infection in low-income countries. Our previous study indicated that the incidences of acute hepatitis B and acute hepatitis C are highest in low SDI regions^[1]. We also added content regarding the PLC burden in high SDI locations in the Prospects subsection of the Discussion section on pages 22, lines 414-423. We hope this added information makes the Discussion section more acceptable.

Reviewer #3:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (High priority)

Specific Comments to Authors: The manuscript entitled " Socioeconomics and attributable etiology of primary liver cancer, 1990–2019" is comprehensive study. Title of article is appropriate. Abstract is good arranged. Introduction is good organized with sufficient literature review. Methods are evidence based. Results show findings clearly. Conclusion is logical and appropriate. References are related to the issue. I think the figures are important and help to better understanding of the subject. The authors have done a good job.

Some minor comments are below to improve the article value:

1. Line 93 do not forget to put Full stop. "...United States."

Response 1: Thank you very much for pointing this out this error. We have added a full stop in the Introduction on page 7, line 101.

2. My concern why did the authors use different year of data such as GBD 2016 for generated the SDI and burden of PLC based on data obtained from GBD 2019. Line 145-149

Response 2: We apologize for the confusion. The method for generating the SDI is described in the report by the GBD 2016 mortality collaborators.^[2] However, up-to-date SDI data, SDI 2019, was employed in this study, as shown in the Appendix, pages 1-15. The sentence in Sociodemographic index subsection of the Materials and Methods section on page 10, lines 152-154, was replaced as follows: “The method of generating SDI is described in the report by the GBD 2016 Mortality Collaborators^[11].” We hope this eliminates the confusion.

3. I thought it is important point if author explained more detail “The global age-standardized incidence rate of PLC caused by hepatitis B reached its peak in 1995–1996 in case of Burden of liver cancer caused by hepatitis B. why it is peak in 1995–1996. It is important to describe in the discussion part.

Response 3: Thank you very much for this suggestion! We added a paragraph to discuss this phenomenon in the Liver cancer subsection of the Discussion section on page 20-21, lines 373-388.

4. Line 330-331: Between 1990 and 2019, the incidence rate of PLC decreased for the high middle SDI locations, it is important point to explained more detail in the discussion part, what going on between 1990 and 2019 so the incidence rate of PLC decreased for the high middle SDI locations?

Response 4: Thank you very much for your keen advice! We discussed this topic in the added paragraph of the Liver cancer subsection of the Discussion section on page 21, lines 386-388 as follows: “Similarly, wide HBV vaccine coverage may have contributed to the declining PLC burden in high middle SDI locations since hepatitis B was the most important attributable etiology of PLC in these regions.”

Reviewer #4:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: This is a good study, precise and acceptable.

Response to Reviewer #4: Thank you very much for your encouragement! We will go through the manuscript before resubmission.

References:

1 **Zeng DY**, Li JM, Lin S, Dong X, You J, Xing QQ, Ren YD, Chen WM, Cai YY, Fang K, Hong MZ, Zhu Y, Pan JS. Global burden of acute viral hepatitis and its association with socioeconomic development status, 1990-2019. *J Hepatol* 2021; **75**: 547-556 [PMID: 33961940 DOI: 10.1016/j.jhep.2021.04.035]

2 **GBD 2016 Mortality Collaborators**. Global, regional, and national under-5 mortality, adult mortality, age-specific mortality, and life expectancy, 1970-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet (London, England)* 2017; **390**: 1084-1150 [PMID: 28919115 PMCID: PMC5605514 DOI: 10.1016/S0140-6736(17)31833-0]