

Peer Review File

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Reviewer A

Comment 1: How do you explain the association of ≥ 65 y.o. with lower risk of IVI ?

Reply 1: Thank you for your comment. Studies have found that young HCC patients are more often associated with aggressive tumor behavior with larger tumor size and higher serum AFP level, which may contribute to a higher macrovascular invasion rate (1,2). Our research found that HCC patients with elevated AFP level were more likely to develop IVI compared to patients with normal AFP level. Moreover, IVI is more common in HCC patients younger than 65 years old. Among all HCC patients, the incidence of IVI was significantly higher in patients younger than 65 years than in patients older than 65 years (59.6% vs. 40.4%).

The phenomenon that young HCC patients are more prone to IVI may involve complex mechanisms, which were not elucidated in our study. Age and AFP are potential risk factors for IVI. Because of the different purposes of the study, we did not explore the correlation between age and AFP. Based on the above statements, our study partially explained the association of patients older than 65 years with lower risk of IVI.

(For the discussions on this issue, we have added them to the discussion part in the manuscript.)

1. Zhang ZY, Guan J, Wang XP, et al. Outcomes of adolescent and young patients with hepatocellular carcinoma after curative liver resection: a retrospective study. *World J Surg Oncol* 2022;20:210.

2. Guarino M, Cucchetti A, Pontillo G, et al; ITA.LI.CA Group. Pattern of macrovascular invasion in hepatocellular carcinoma. *Eur J Clin Invest* 2021;51:e13542.

Changes in the text: We have supplemented the discussion on this issue, see line 369-383 on page 17-18.

Comment 2: Which histological grading system was use in the study ?

Reply 2: Thanks a lot for the comment. In the SEER database, grading and differentiation codes are defined according to The International Classification of Diseases for Oncology, Second Edition (ICD-O-2). Histological grade of liver cancer in the database is divided into five categories, of which grade I refers to well differentiated, grade II refers to moderately differentiated, grade III refers to poorly differentiated, and grade IV refers to undifferentiated.

Changes in the text: To clarify the histological classification of HCC, we have added an explanation to the methods section of the manuscript, see lines 138-141 on page 7.

Reviewer B

Comment1: This article would require proofreading and editing by someone fluent in English.

Reply1: Thank you for your comment. We have made some changes in the manuscript. If our manuscript were accepted, we would invite experts who are fluent in English to revise it.

Changes in the text: See the manuscript for details of changes.

Comment 2: The main weakness of their work is that the nomogram created only takes into account macroscopic vascular invasion that can be easily diagnosed by imaging and therefore with little impact when it comes to therapeutic management. It would be more interesting to study microscopic vascular invasion, which can only be diagnosed by histological examination. I suggest that they obtain these new data and add them to the manuscript.

Reply 2: Thank you for giving us such valuable opinions. We agree with your opinions because what you mentioned is also what we intend to study. Unfortunately, due to the limitation of SEER database design, the SEER database does not include microvascular invasion as a separate type of vascular invasion, which makes it impossible for us to obtain this part of data. In the SEER database, the classification of vascular invasion mainly includes intrahepatic vascular invasion, macroscopic vascular invasion and vascular invasion not stated. Therefore, we only studied the risk and prognosis of intrahepatic vascular invasion in patients with hepatocellular carcinoma. In the future, we may need to collect data of HCC patients with microvascular invasion to provide a more reliable basis for assessing the prognosis of HCC patients.

Changes in the text: None