Peer Review File
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Reviewer A

Authors reported, "Clinical features and prognostic factors of patients with inoperable hepatocellular carcinoma treated with chemotherapy: a population-based study". This manuscript contains important findings for treatment options for patients with hepatocellular carcinoma. However, I think that there are some concerns, as below.

Major comments:
Comment 1: Whether patients with HCC are operable or inoperable is mainly determined by tumor stage, PS, and liver function. Since this is determined according to generally common criteria worldwide, it is inappropriate to analyze “risk factors” for inoperability using data at the initiation of treatment.
Reply 1: Thank you for your comments. We appreciate your input, as most international guidelines on liver cancer do highlight the factors you mentioned. However, the SEER database does not include the relevant indicators, such as performance status (PS) and liver function. In our research, we classified patients who did not undergo surgery based on the recommendations in the SEER database (see code 'Reason no cancer directed surgery' in SEER, Page 6, lines 178-180). We acknowledge that the factors you mentioned are indeed crucial for accurately determining which patients need surgery, and this is one of the limitations of our study. We noted that several liver cancer studies using the SEER database (PMID:37106014; PMID:37409255; PMID:30854126) did not mention liver function and similar indicators. This highlights a common limitation in research using the SEER database, underscoring the need for more comprehensive data collection to enhance the accuracy of patient assessment and treatment planning.

Comment 2: The details of the treatment are unclear. You showed that 30% or more of the patients in the operable group received chemotherapy. Is this NAC or adjuvant chemotherapy? Or does this mean that the disease relapsed after surgery and chemotherapy was introduced at some point?
Reply 2: Thank you for your comments. All patients received adjuvant chemotherapy instead of neoadjuvant chemotherapy. Additionally, patients with the disease relapsed after surgery and chemotherapy was not included in research.
Changes in the text: Based on your suggestions, we have made changes in the article (see Page 7, line 185-187).

Comment 3: The same is applied for the with/without chemotherapy group. It is unclear whether this means that the initial treatment of inoperable HCC was chemotherapy or that chemotherapy was introduced at some point, even once. If the latter is the case, it is not surprising that patients with inoperable HCC who were

treated with local therapy at an early tumor stage and later received chemotherapy when they reached an advanced stage would have a better prognosis than patients with advanced HCC for whom chemotherapy had to be the first choice.

Reply 3: Thank you for your comments. Our research is divided into three parts, with the second part focusing on the positive prognostic value of adjuvant chemotherapy in inoperable HCC, demonstrating its significant improvement in patient prognosis. We classified the patients into two groups based on whether they received chemotherapy or not.

However, due to the limitations of the SEER database, we are unable to determine the timing and number of chemotherapy cycles that patients received. To address potential confounding factors, we performed a 1:1 propensity score matching (PSM) analysis between the two groups. This approach aimed to minimize the impact of baseline differences between the groups, thereby allowing us to assess the prognostic value of chemotherapy more accurately in inoperable HCC patients. Additionally, it is important to note that none of the patients in our study received local therapy. This aspect helps to isolate the effect of chemotherapy on patient outcomes without the confounding influence of local treatments.

Comment 4: There is no mention of hepatic reserve in this study. Liver function is also defined as an important factor in global treatment standards and should be considered.

Reply 4: Thank you for your comments. Liver function is indeed an important prognostic factor in the study of liver cancer. However, as mentioned previously, the SEER database does not include data on liver function. In our study, we predicted patient prognosis based on available data in the SEER database, such as tumor stage, and subsequently developed a nomogram prediction model. This model has demonstrated good predictive efficiency.

This approach is similar to the methodologies used in other studies (PMID:36798659; PMID:37365056; PMID:37266663). To further enhance our research, we plan to construct a large-sample, multi-center prospective study in the future. This will allow us to include more comprehensive data, including liver function, to improve the accuracy and robustness of our prognostic predictions.

Reviewer B

This study addresses a current topic.

The manuscript is quite well written and organized. English could be improved.

Figures and tables are comprehensive and clear.

The introduction explains in a clear and coherent manner the background of this study.

We suggest the following modifications:

Introduction section

Comment 1: Although the authors correctly included important papers in this setting, we believe a couple of studies should be cited within the introduction (PMID: 33508960; PMID: 36533070; PMID: 36579504; PMID: 36695827), only for a matter of consistency. We think it might be useful to introduce the topic of this interesting study.

Reply 1: Thank you for your comments. We have read the articles you have provided and selected three of them for reference. In addition, our research has been modified and supplemented according to the content of these articles.

Changes in the text: Based on your suggestions, we have made changes in the article (see Page 4, line 109-118).

Comment 2:

·Discussion section: Very interesting and timely discussion. Of note, the authors should expand the Discussion section, including a more personal perspective to reflect on. For example, they could answer the following questions – in order to facilitate the understanding of this complex topic to readers:

What potential does this study hold?

Reply 2: Thank you for your comments. In our study, we explored and analyzed inoperable hepatocellular carcinoma (HCC). The research is divided into three readable parts. Firstly, we investigated independent risk factors related to inoperable HCC, such as advanced TNM stage and positive pretreatment AFP levels. These factors help identify patients at higher risk and provide insight into the disease's progression. The second part focuses on the positive prognostic value of adjuvant chemotherapy in inoperable HCC. Our findings indicate that adjuvant chemotherapy can significantly improve patient prognosis, underscoring its importance in the treatment regimen for inoperable HCC patients. Finally, we established a nomogram prediction model to estimate the survival probability of patients with inoperable HCC receiving chemotherapy. This model serves as a valuable tool for assisting doctors in making clinical decisions, particularly regarding the use of chemotherapy. The aim of our study is to help clinicians treat patients with inoperable HCC more effectively and to assist them in making more informed clinical decisions. By identifying key risk factors, demonstrating the benefits of adjuvant chemotherapy, and providing a practical prediction model, we hope to contribute to the optimization of therapeutic strategies and the improvement of patient outcomes.

Changes in the text: Based on your suggestions, we have made changes in the article (see Page 10, line 289-297).

Comment 3: What are the knowledge gaps and how do researchers tackle them?

Reply 3: Thank you for your comments. Some limitations of our study should be noted. First, we employed a retrospective design using data collected from a public database, making selection bias inevitable. Additionally, the SEER database lacks critical variables such as liver function parameters (e.g., liver enzymes, bilirubin

levels, albumin levels), comorbid conditions (e.g., jaundice, ascites, hepatic encephalopathy), and imaging data. Furthermore, details of the chemotherapy regimens, including information on specific drugs and administration methods, were not clearly outlined.

To verify our findings, prospective and randomized controlled studies are needed. Consequently, we plan to construct a large-sample, multi-center prospective study in the future to enhance our research. This approach will allow us to incorporate a more comprehensive set of variables and provide a more robust analysis of the factors influencing the prognosis of inoperable HCC patients.

Comment 4: How do you see this area unfolding in the next 5 years? We think it would be extremely interesting for the readers.

Reply 4: Thank you for your comments. In the next five years, with the increasing number of inoperable HCC patients, improving therapeutic efficacy and optimizing prognosis will become urgent challenges for doctors. Consequently, survival prediction models have emerged as excellent auxiliary methods.

It should be noted that future treatment methods will continue to evolve and improve, including combination therapies such as ICIs combined with chemotherapy, and TACE combined with chemotherapy. Therefore, it will be essential to update the indicators used in survival prediction models and the methodologies for establishing these models to accommodate various treatment modalities.

Despite these advancements, chemotherapy will likely continue to play a crucial role in the treatment of inoperable HCC. Thus, our study remains valuable and can provide important insights and assistance to future researchers. By continually refining our models and incorporating new treatment data, we can enhance the precision and applicability of survival predictions, ultimately improving patient outcomes.

Changes in the text: Based on your suggestions, we have made changes in the article (see Page 13, line 365-374).

Comment 5:

However, we think the authors should be acknowledged for their work. In fact, they correctly addressed an important topic in HCC, the methods sound good and their discussion is well balanced.

One additional little flaw: the authors could better explain the limitations of their work, in the last part of the Discussion.

Reply 5: Thank you for your comments. The study is based on the seer database, so there are some unavoidable flaws, such as the liver function mentioned above. Therefore, some limitations to our study should be mentioned. First, we employed a retrospective design with data collected from a public database, and selection bias was inevitable. Moreover, the SEER database lacks critical variables such as liver function parameters (liver enzymes, bilirubin levels, albumin levels), comorbid conditions (jaundice, ascites, hepatic encephalopathy), and imaging data. Finally, the details of the chemotherapy regimens, including information on specific drugs and

administration methods, were not clearly outlined. Prospective and randomized controlled studies are needed to verify our findings. All the above are mentioned in the article (see Page 13, line 375-381).

We believe this article is suitable for publication in the journal although major revisions are needed. The main strengths of this paper are that it addresses an interesting and very timely question and provides a clear answer, with some limitations.
We suggest a linguistic revision and the addition of some references for a matter of consistency. Moreover, the authors should better clarify some points.