

## Peer Review File

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### Reviewer A

**Comment 1:** The title needs to indicate the clinical research design of this study, i.e., a retrospective cohort study.

**Reply 1:** We have added "a retrospective cohort study" behind the title  
Changes in the text: line 3 high-light parts

**Comment 2:** The background of the abstract did not describe the clinical significance of this research focus, the methods did not describe the inclusion of subjects, follow up procedures, prognosis outcomes and clinical covariates, and main statistical methods for assessing the independent prognostic role of HS-mGPS score, the results need to briefly describe the clinical characteristic of the study sample and quantify the findings on the prognostic roles such as HR and accurate P values, and the conclusion needs comments for the clinical implications of the findings.

**Reply 2:** We have modified the abstract base on the comment  
Changes in the text: line 28-58 high-light parts

**Comment 3:** In the introduction of the main text, the authors need to extensively review known prognostic factors and biomarkers in ICC and its subtypes, analyze the limitations of prior studies, and explain the clinical needs of focusing on HS-mGPS score. The methodology of the main text needs to describe the sample size estimation procedures, accurately describe the clinical research design, and data collection of baseline clinical covariates. In statistics, please describe the details of the test of the independent prognostic role of HS-mGPS score. In particular, how the statistically compare the prognosis roles between GPS and HS-mGPS.

**Reply 3:** We add the review for known prognostic factors and biomarkers in ICC and modified the study design, describe the whole procedures. And we add the description of the test of the independent prognostic in the method. A new roc curve figure for statistically compare the prognosis roles between GPS and HS-mGPS was included in the result.

Changes in the text: introduction: line 116-126 high-light parts; methodology: 134-136, 145-152; statistics: 169-175; 222-224

**Comment 4:** Please ensure  $P < 0.05$  is two-sided. Please consider to cite several related papers...

**Reply 4:** We ensure  $p < 0.05$  is two-sided and we added in the statistics part. And we cite 1, 4, 5 paper in our manuscript.

Changes in the text: introduction: line 72 90 94 175 high-light parts

### Reviewer B

1. Please check through your article to make sure **all** the abbreviated terms have been defined when they **FIRST** appear in the Abstract and the main text. "HR" "CI" in the abstract and "CA19-9" "BMI" "CEA" "ROC" "HR" "CI" in the main text for example.

**Reply:** we have gone through the whole article and define all abbreviation

2. Please check if any reference should be added since you mention “studies”.

“And in our earlier **studies** on LD-type ICC, we also found that the two subtypes of ICC exhibited different nutritional and metabolic profiles[10].”

“Some **studies** suggest that the number of lymph node metastases can affect prognosis, but more real-world evidence is needed to confirm this.[11]”

**Reply:** that’s really sorry about the mistake. Actually there is no other reference would be added for that is our wrong stating. We have change it in the manuscript

3. Figures and Tables

- **All abbreviations** in figures/tables and legends should be explained. “ICC” “CRP” “ALB” in Figure 1, and “mGPS” in Table 2 for example. Please check all abbreviations and provide the full names in the corresponding legend.

**Reply:** we have gone through the paper and check all abbreviations and provide the full names in the manuscript.

- Please indicate the meaning of the circles and arrows in Figure 2 legend.

**Reply:** We have added the description for the arrow and circle in figure2

- Figures should be cited **consecutively** in the text and numbered in the order in which they are discussed. Thus, the first citation of Figure 3a should be right after Figure 2. Please check and revise.

**Reply:** We have changed the order of figure2 and figure3 so it could be cited consecutively.

- **It is suggested to unify the description in Figure 3b and its legend.**

→ **Big duct**

“(b) Differences in overall survival between **large duct-type** and small duct-type patients.”

**Reply:** We have revised the description in figure 3b.

- Please check whether it should be “Figure 4G-4I”.

“And it showed no correlation for GPS(p=0.78), mGPS(p=0.93) and even HS-mGPS(p=0.98; figure4,h, i and j) with prognosis.”

**Reply:** It is our mistake and we have changed the description of citation of figure in the whole manuscript

- Please add description for the y-axis in Figure 5b.

**Reply:** description for the y-axis in Figure 5b was added.

- Please check whether it should be “HS-mGPS” in Figure 5.

— Hs-GPS (AUC=0.624)

**Reply:** we have revised in Figure 5.

- Please check whether it should be superscript in Table 1.

AKP,U/L2

GGT,U/L2

**Reply:** we have revised in Table 1.

- Please double check the data in Table 1.

Tumor differentiation <sup>1</sup>	
Well	12 (6.5%)
Moderately	147 (79%)
Poor	26 (14%)
T <sup>1</sup>	
1	103 (56%)
2	58 (31%)
3	22 (12%)
4	2 (1.1%)

**Reply:** Truly sorry about the mistake we made! For table 1, we change the superscript after AKP and GGT. All the percentages were unified to keep to integer.

- The data of “Nx” is missing in Table 1.

**Reply:** we add the data of “Nx” of Table 1.

- Please double check the full name of “WBC” in Table 1 and Table 5, 6.

Abbreviations: **WBC**, white blood count;

- It is suggested to unify the full name of “GGT” in Tables and the text.

**aminotransferase; AKP, Alkaline Phosphatase; GGT, γ-glutamyl transpeptidase; LDH, Lactate Dehydrogenase; CA199, Carbohydrate**

**hemoglobin, gamma-glutamyl transferase (GGT), alanine aminotransferase**

**Reply:** The full name of WBC and GGT were also unified.

- There is no “TNM” in Table 1, while it is explained in Table 1 footnote.

**Reply:** For our mistake, we missed the name of “TNM” in table 1 as to match the footnote.

- Please unify “CA199”, “CA-199” and “CA 19-9” in Table 1, 5, 6 and the text.

**Reply:** we had unified the statement of “CA-199” and changed through the whole paper. Highlighted content associated with table1 were change based on table1.

- Please double check the highlighted content in the following sentence, they are inconsistent with Table 1.

“Among the 185 patients who underwent curative resection for ICC, the median age was 64 years, and 49% were male. The median tumor size was 5.0 cm, with a median CA 19-9 level of 65 ng/ml.”

“Notably, 27% presented with multiple nodules, and 24% had evidence of microvascular invasion. The median levels of albumin, CRP, and CEA were 40.2 g/L, 5 g/L, and 3.19, respectively.”

**Reply:** we had revised the baseline description base on table1

- Please check whether it should be “CI” in Table 2-4.

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**95% CL** ←

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**Reply:** we had revised it in Table 2-4

- Please revise “Hs-mGPS” to “HS-mGPS” in Table 2 and 3.

**Reply:** we had revised them in Table 2,3

- Please revise “p-value” to “P value” in Table 2-5.

**Reply:** we had revised them in Table 2-5.

- Please unify the data in Table 2 and the text.

“Moreover, subtypes classification emerged as an independent predictor of OS (HR=1.76,95%CI=1.04-2.99, P=0.036; table2).”

**Reply:** we had revised them in text.

- Please double check the highlighted content in the following sentence, they are inconsistent with Table 3.

“Through multivariate Cox regression analysis, we identified HS-mGPS as an independent risk factor for overall survival (HR=2.1, 95% CI=1.017-4.374, p=0.049), whereas GPS and mGPS was only positive in univariate analysis. In addition to tumor subtype, T stage (HR=2.20, 95% CI=1.225 - 3.08, p<0.001), and abnormal AKP (HR=1, 95% CI=1 - 1.003, p=0.044) levels are also independent risk factors for ICC. (table3)”

**Reply:** The highlighted content associated with table3 was an incorrect cite of table, and we have changed it table2.

- The data are the same in Table 4?

Univariate analysis			Multivariate analysis		
HR	95% CL	p-value	HR	95% CL	p-value
1.95	1.205 - 3.147	0.006	1.95	1.205 - 3.147	0.006

**Reply:** We have double checked the data. The data of table4 are currently the same. Because T stage is the only one univariate positive indicator. As it enrolled into the multivariate, there is no other variate to compared. So that the data is the same.

- Please add unit for “Age” in Table 5 and 6.

**Reply:** we had added it in Table 5 and 6.

- Please double check the superscript of “p-value” in Table 5.

**p-value<sup>2</sup>**

**Reply:** we had deleted it

- Please double check the data of “Membrane invasion”, “G batts.” and “S Batts.” in Table 5, whether they should be reversed.

Characteristic	Large Duct type, N = 57	Small duct type, N = 128
Membrane invasion <sup>1</sup>		
0	81 (69%)	33 (69%)
1	20 (17%)	8 (17%)
2	16 (14%)	6 (13%)

**Reply:** It’s our mistake that we put on the data incorrectly. The data of “Membrane invasion” and “G batts.” and “S Batts.” Were reversed and some of them were modified as we check the original data, no conclusion was changed.

- There is no “CAR, NLR, PLR, LCR, Hs-mGPS, GPS” in Table 5, while they are explained in Table 5 footnote.

**Reply:** We have gone through the footnote and removed the unnecessary footnoted and superscript.

- There is no “LP, CAR, NLR, PLR, LCR” in Table 6, while they are explained in Table 6 footnote.

**Reply:** We have gone through the footnote and removed the unnecessary footnoted

and superscript.

- Please check if the superscript need to be removed in Table 6.

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**0, N = 301**↵

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**Reply:** We have removed it

- Please revise “NX” to “Nx” in Table 6.

**Reply:** We have revise it

- Please double check the P value in the following sentence.

“The LD and SD types not only show higher in CA-199 also in AST, ALT, and GGT (P=0.01, P=0.002, P<0.0001, table5) which was usually shows higher in LD-types.”

**Reply:** We have changed the P value in the sentence.

- Please double check the highlighted content in the following sentence, they are inconsistent with Table 6.

“We found that the score 2 patients in SD-types had significantly higher in ALT, AKP, AST, GGT and LDH (p=0.022, 0.002, 0.008, <0.001, and 0.006).”

“But except gender(p=0.041), there was still no any positive sign for LD-types.”

**Reply:** We have modified the text base on table 6.