

Peer Review File

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Reviewer A

The paper titled “A surgical nursing perspective analysis of glucose variability in hepatocellular carcinoma patients with BCLC B-C stage within 1 year of hepatectomy: a retrospective cohort study from 2016 to 2020” is interesting. Compared to the patients without T2D, the HCC patients with T2D in BCLC stage B-C showed greater variability in glucose levels within 1 month and 1 year of surgery. However, there are several minor issues that if addressed would significantly improve the manuscript.

In the introduction of the manuscript, it is necessary to clearly indicate which metabolic parameters of diabetes are associated with HCC.

Reply: We have added metabolic parameters of diabetes are associated with HCC in the introduction of the manuscript following review opinion.

What are the prognostic factors for patients with BCLC B-C stage HCC? It is recommended to add relevant content.

Reply: We have added relevant content about the prognostic factors for patients with BCLC B-C stage HCC.

The introduction part of this paper is not comprehensive enough, and the similar papers have not been cited, such as “Diabetes mellitus and postoperative blood glucose value help predict posthepatectomy liver failure in patients with hepatocellular carcinoma, J Gastrointest Oncol, PMID:34790399”. It is recommended to quote this article.

Reply: We have added it following review opinion.

The abstract is not sufficient and needs further modification. The research background did not indicate the clinical needs of the research focus.

Reply: We have re-edited the abstract following review opinion.

Does hyperglycemia increase the incidence of surgical site infections? What is the possible mechanism? It is recommended to add relevant content.

Reply: We have relevant content about hyperglycemia increase the incidence of surgical site infections and possible mechanism following review opinion.

What are the highlights and significance of this study? What is the author's next research plan? It is recommended to add relevant content to the discussion.

Reply: We have relevant content in the discussion following review opinion.

There are many uncertainties in retrospective research, which increase the deviation of research results. How to explain and solve this problem?

Reply: Having a large sample size and add Bias analysis is one of the best ways to solve the problem. We will supplement these deficiencies in the discussion section of the paper.

Reviewer B

First, in the title the authors need to indicate the comparisons between patients with and without T2D.

Reply: we have re-edited it following review opinion.

Second, the abstract needs some revisions. The background did not indicate the clinical significance of this research focus. The methods need to describe the inclusion of subjects, the measurement of blood glucose and frequency of the measurement, follow up procedures, and statistical methods for calculating the variability in blood glucose levels. The results need to first briefly summarize the clinical characteristics of the two groups and report their baseline comparability. The conclusion should not repeat the main findings and please have comments for the clinical implications of the findings.

Reply: we have re-edited the abstract following review opinion.

Third, in the introduction of the main text, the authors need to have a brief review on known factors associated with the variability in glucose and what the clinical significance of this research focus is. I cannot see the clinical contribution of the comparisons of the variability between the two groups.

Reply: We have added corresponding content following review opinion.

Fourth, in the methodology of the main text, please accurately describe the clinical research design, sample size estimation, follow up procedures, and importantly, details of blood glucose measurements including frequency. The authors also need to describe the measurement of demographic and clinical factors. In statistics, please describe the details of the calculation of variability including SD and CV. The authors must be aware of that SD is also a measure of variability (i.e., PMID 25449513). Please ensure $P < 0.05$ is two-sided. The authors need to first test the baseline comparability of the baseline between the two groups. Please describe the multiple regression methods to adjust for the baseline factors between the two groups. “with our without T2D” should be “with or without T2D”. In discussion, please describe the limitations caused by no standardized procedures for the measurements of the blood glucose levels in this study.

Reply: We have re-edited it following review opinion.

Reviewer C

This study investigated the variability of glucose in hepatocellular carcinoma patients with BCLC B-C stage. The topic is novel and interesting. I have some comments.

1. Two ethics committees have approved this study. The Ethics committee approval number and date should also be stated.

Reply: Thank you for your suggestion and we have added it following review opinion.

2. A flowchart should be used to depict the patient selection process.

Reply: Thank you for your suggestion and the description of experimental methods can replace the flowchart.

3. The manuscript should be organized following the STROBE guideline.

Reply: Thank you for your suggestion and we have organized following the STROBE guideline following review opinion.

4. The authors analyzed the relationship between glucose variability and their clinical characteristics with the Spearman analyses. I suggest the authors perform multiple variable linear regression analysis.

Reply: Thank you for your suggestion. The statistical methods in the original paper are also applicable to research.

5. Some variables in Tables 4 and 5 are confusing. For example, the authors investigated the relationship between “taking insulin at time of surgery” and “glucose variability” with the Spearman analysis. Taking insulin at the time of surgery is a binary variable. How to

analyze its relationship with glucose variability with the Spearman analysis?

Reply: We have corrected this error.

6. The conclusion section of the abstract. The conclusion is incomplete. Factors that affect glucose variability should be reported.

Reply: We have added affect glucose variability in the conclusion section of the abstract following review opinion.

7. Some clinical details were extracted from the medical records of the participants. Please specify the time point of data extraction. On admission or after surgery?

Reply: We have added it following review opinion.

8. The limitation of this study should be discussed in the discussion section.

Reply: We have added the limitation of this study in the discussion section.

9. Methods in the abstract section: the methods used to analyze factors affecting glucose variability should be reported.

Reply: We have added it following review opinion.

10. In the discussion section, the authors only discussed the possible mechanisms of glucose variability in HCC patients. The clinical implications of their findings should be discussed.

Reply: We have added the clinical implications of our findings following review opinion.

Reviewer D

1. Reference 27 and 28 are the same one. Please check and revise.

Response: thank you for your review and we have re-edited it following review opinion.

2. Table 1:

The symbol a cannot be found in your Table 1, but you indicated it in the table footnote.

Please check.

520 a Patients with diabetes vs. patients without diabetes by Mann-Whitney U,
521 chi-squared (χ^2), or Fisher's exact tests; Note: N=95. IQR=interquartile range;

Response: thank you for your review and we have added it following review opinion.

3. Table 2:

- 1) Please check whether there are any unit for these variables.

Steroid dose over 1 month following surgery, prednisolone equivalent,

median [IQR]

Steroid dose over 12 months following surgery, prednisolone equivalent,

median [IQR]

Antibiotic use over 12 months, n

Response: thank you for your review and we have added it following review opinion.

2) Please indicate the full name of “BCLC” and “IQR” in the table footnote.

Response: thank you for your review and we have added it following review opinion.

4. Table 3:

Is there any meaning for #?

Mean # of glucose measurements (n) ^{b,c}		
1 month ^c	33[13.5–46.50] (n=30) ^c	7[4.50–12.0] (n=65)
1 year ^c	46.5[23.50–69.50] (n=30) ^c	22.5[11.00–46.50] (

Response: thank you for your review and we have re-edited it following review opinion.

5. Table 4:

The below data in your main text are inconsistent with Table 4.

192 **Table 4** shows the Spearman correlation coefficients for variability in glucose levels
 193 and the demographic and clinical characteristics of the patients with T2D. In the T2D
 194 patients, a higher 1-month SD was correlated with a lower cumulative dose of steroids
 195 ($r=-0.645$, $P<0.01$) and a lower baseline body mass index (BMI) ($r=-0.431$, $P<0.05$)
 196 within 1 year of surgery, and administering insulin during surgery ($r=0.335$, $P<0.05$).
 197 A correlation was found between a higher 1-month CV and a lower baseline BMI
 198 ($r=-0.464$, $P<0.001$). Additionally, correlations were found between a higher 1-year

BMI ^c	-0.077 ^c	-0.431* ^c	-0.464** ^c	0.062 ^c	-0.235 ^c	-0.336 ^c
Gender ^{a,c}	0.361 ^c	0.243 ^c	0.192 ^c	0.452** ^c	0.368* ^c	0.136 ^c
Employment status ^{b,c}	0.016 ^c	-0.112 ^c	-0.155 ^c	0.078 ^c	0.162 ^c	0.161 ^c
Marital status ^c	-0.235 ^c	-0.162 ^c	-0.123 ^c	-0.328 ^c	-0.339* ^c	-0.225 ^c
Median household income ^c	0.135 ^c	0.024 ^c	-0.063 ^c	0.123 ^c	0.236 ^c	0.192 ^c
Preoperative glucose ^c	0.322 ^c	0.192 ^c	0.037 ^c	0.505** ^c	0.435** ^c	0.292 ^c
Preoperative glucose > 140 mg/dL ^c	0.298 ^c	0.135 ^c	0.064 ^c	0.436** ^c	0.423** ^c	0.265 ^c
Cumulative steroid dose 1 month following surgery ^c	-0.250 ^c	-0.230 ^c	-0.105 ^c	-0.436 ^c	-0.288 ^c	0.123 ^c
Cumulative steroid dose 1 year following surgery ^c	-0.636** ^c	-0.645** ^c	-0.252 ^c	-0.298 ^c	-0.305 ^c	0.064 ^c
Taking insulin at time of surgery ^c	0.359* ^c	0.355* ^c	0.196 ^c	0.343* ^c	0.286 ^c	0.164 ^c

Response: thank you for your review and we have re-edited it following review opinion.