

Dear Editors and Reviewers,

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled "**Endoscopic submucosal tunnel dissection for early esophageal squamous cell carcinoma in patients with cirrhosis: a propensity score analysis**" (Manuscript NO.78391). We have addressed each comment raised by the reviewers and hope this revised manuscript is now acceptable. Each concern is discussed in detail below. We have revised the paper, and would like to re-submit it for your consideration. The amendments are indicated within the revised manuscript using track changes, as requested in the journal's guidelines.

Thank you for allowing us to resubmit our manuscript for your consideration.

Sincerely,

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Reviewer #1: This article requires minor language polishing rest is fine.

Answer: Dear professor, thank you for your suggestion. The manuscript has been polished by an English language editing company.

Reviewer #2:

1. The endoscopy used for evaluation is not clear. There are several types of endoscopes for evaluation of early esophageal cancer. Also, the NBI (narrow-band imaging) and LCI (linked color imaging) certain benefits for detecting esophageal cancer. Please describe the specific method for evaluating esophageal cancer by endoscope (Gruner et al. Endoscopy. 2021 Jul; 53(7): 674-682; Nakamura et al. Esophagus. 2021 Jan;18(1):118-124).

Answer: Dear professor, thank you for your suggestion. We have added the detailed information regarding the evaluation of early esophageal cancer, and the revision contents could be found in the “**Pre-ESTD evaluation**” section, Line 154-159, Page 8.

2. The definition of “experienced endoscopists” is not clear. Please specify this point.

Answer: Dear professor, thank you for your suggestion. The definition of “experienced endoscopists” has been added, and the detailed information can be found in the “**ESTD procedure**” section, Line 180-181, Page 9.

3. The authors performed the propensity score matching in the results section. The matching method (Caliper width, matching ratio) should be described

(Reiffel et al. Am J Med. 2020 Feb;133(2):178-181).

Answer: Dear professor, thank you for your suggestion. Detailed information on the matching method has been added. These revisions could be found in the “**Statistical analysis**” section, Line 245-247, Page 12.

4. In table 1, some background data is missing. The data of the knife and hemostatic forceps used in the procedure should be described (Although the authors described in the 2.3 ESTD procedure section, it is not reasonable that 2 knives and 2 hemostatic forceps were used during the one ESTD procedure).

Answer: Dear professor, thank you for your advice. The missing background data were added in the “**Baseline characteristics**” section, and the inappropriate description of endoscopic accessories has also been corrected in the “**ESTD procedure**” section. The revised contents could be found in Line 266-267, Page 13 and Line 185-187, Page 9.

5. The background data of the cirrhotic patients should be clearly described. The data of the Child-Pugh score (Median and distribution), serum albumin, and other factors associated to the grading of the Child-Pugh score, or MELD scores should be described. These data is essential to discuss whether decreased overall survival is reasonable in this cirrhotic patients cohort.

Answer: Dear professor, thank you for your advice. The missing data of the factors associated to the grading of the *Child-Pugh* score have been added, which could be found in “**Table 2**” and “*Characteristics of patients with*

cirrhosis" section, Line 277-279, Page 13.

6. "p=0.000" is not commonly used for expressing "Statistically significant."

The "p=0.000" seems that the statistics is not performed for the comparison of 2 groups. The authors should describe $p < 0.01$ or actual p-value for describing "Statistically significant."

Answer: Dear professor, thank you for your suggestion. The corrected contents could be referred to in "Table 1" and "*Baseline characteristics*" section, Line 247, 266, 274, Page 13.

7. The overall survival data must be described as median overall survival (months or days). It is not clear that time point evaluated the percentage of overall survival in the main text.

Answer: Dear professor, thank you for your kind proposal. Since there were fewer deaths during follow-up in both groups, we were unable to calculate the median overall survival. In addition, limited by the small sample size and *the* number of deaths, we were also unable to correctly calculate the survival at a specific time point. Therefore, we hope you can agree with our current expression of survival rate.

8. The authors stated that the costs and duration of hospitalization were statistically longer in the cirrhotic patients group. However, the more costs should be offered when the patients stayed longer in the hospital. The authors should perform multivariate analysis to exclude that the costs and duration of hospitalization is independently associated with liver cirrhosis.

Answer: Dear professor, thank you for your suggestion. According to your suggestion, binary logistic regression analysis has been performed, and the relevant modifications can be found in the “**Statistical analysis**” section, “**Perioperative Outcomes**” section, and “**DISCUSSION**” section, Line 233-238, Page 11; Line 306-310, Page 15 and Line 371-373, Page 18.

9. From figure 4, decrease survival in the cirrhotic patients were observed in relatively early days after the ESTD (between 0-40 months). From this point of view, it is questionable whether the cirrhotic patients should be received ESTD. The medial overall survival received chemoradiation therapy in the stage I esophageal cancer was around 80 (Kato et al. Jpn J Clin Oncol. 2009 Oct;39(10):638-43).

Answer: Dear professor, thank you for your suggestion. We believe that patients with early esophageal cancer coexisting with cirrhosis should undergo ESTD based on the following viewpoints: ①EEC usually has a good prognosis after endoscopic resection, with a reported 5-year survival rate of more than 90%, thus, it is worth exerting effort for endoscopists to try it. ②The most predominant cause of death during follow-up in our study was not due to ESTD or esophageal cancer but rather cirrhosis-related complications, such as hepatic encephalopathy. ③If esophageal cancer patients with liver cirrhosis receive chemoradiation therapy, cirrhosis-related complications will also happen. In addition, patients with liver cirrhosis often have a poor liver function, which affects the implementation of radiotherapy and

chemotherapy, and are prone to cause complications related to liver cirrhosis or radiotherapy and chemotherapy.

Therefore, we hope you can agree with us.

10. This study is retrospective study, and the certain bias could not be excluded. For reaching conclusion that the esophageal ESTD can be safely and effectively performed in patients with liver cirrhosis, the comparison between ESTD and ESD in the cirrhotic patient's cohort should be performed. Please consider to discuss this point.

Answer: Dear professor, thanks for your suggestion. In our center, ESTD is a preferred endoscopic resection method for the treatment of early esophageal cancer; thus, we have little data on ESD for esophageal cancer patients with cirrhosis. Therefore, the comparison between ESTD and ESD in the cirrhotic patient's cohort cannot be performed in our study.

11. The hemoglobin unit should be described as g/dl, according to the original article (Kim et al. Eur J Gastroenterol Hepatol. 2007 May;19(5):409-15).

Answer: Dear professor, thank you for your advice. We have corrected the incorrect unit writing in the "*Outcome measures*" section, Line 218, Page 11.

12. The authors used SPSS for statistical analysis. Please describe manufacturer and originated country of the SPSS.

Answer: Dear professor, thank you for your advice. The detailed manufacturer information of SPSS has been added in the "**Statistical analysis**"

section, Line 241, Page 12.

13. The method used for evaluating gastroesophageal varices should be described in the “Patients and methods” section.

Answer: Dear professor, thank you for your advice. The method used for evaluating gastroesophageal varices has been described in the “**Pre-ESTD evaluation**” section, Line 155-159, Page 8.

EDITORIAL OFFICE’S COMMENTS

Science editor: The manuscript has been peer-reviewed, and it's ready for the first decision. Language Quality: Grade B (Minor language polishing).

Scientific Quality: Grade D (Fair)

Answer: Dear editor, thank you for your suggestion. We have polished and revised the English writing language. The editing certificate is shown in the annex (78391-Non-Native Speakers of English Editing Certificate).

Company editor-in-chief: I recommend the manuscript to be published in the World Journal of Clinical Cases. Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the Reference Citation Analysis (RCA). RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the author,

"Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at: <https://www.referencecitationanalysis.com/>.

Answer: Dear editor, thank you for your suggestion. In our study, we have cited the latest highlight articles.

ROUND 2

Comment: The manuscript has been revised well. I agree that the manuscript described the significance of ESTD for hepatic cirrhosis patients. I think this manuscript will be potentially acceptable after some correction have been done. I hope my comments would help to improve the quality of this article. 7. The overall survival data must be described as median overall survival (months or days). It is not clear that time point evaluated the percentage of overall survival in the main text. **Answer:** Dear professor, thank you for your kind proposal. Since there were fewer deaths during follow-up in both groups, we were unable to calculate the median overall survival. In addition, limited by the small sample size and the number of deaths, we were also unable to correctly calculate the survival at a specific time point. Therefore, we hope you can agree with our current expression of survival rate. The authors stated that median overall survival (OS) could not be calculated because of the fewer

deaths during follow-up period. However, the median OS estimation should be performed using Kaplan-Meier method and if less than 50% of the patients did not reach the endpoint, the authors should clearly state that point. 9. From figure 4, decrease survival in the cirrhotic patients were observed in relatively early days after the ESTD (between 0-40 months). From this point of view, it is questionable whether the cirrhotic patients should be received ESTD. The medial overall survival received chemoradiation therapy in the stage I esophageal cancer was around 80 (Kato et al. Jpn J Clin Oncol. 2009 Oct;39(10):638-43). Answer: Dear professor, thank you for your suggestion. We believe that patients with early esophageal cancer coexisting with cirrhosis should undergo ESTD based on the following viewpoints: ①EEC usually has a good prognosis after endoscopic resection, with a reported 5-year survival rate of more than 90%, thus, it is worth exerting effort for endoscopists to try it. ②The most predominant cause of death during follow-up in our study was not due to ESTD or esophageal cancer but rather cirrhosis-related complications, such as hepatic encephalopathy. ③ If esophageal cancer patients with liver cirrhosis receive chemoradiation therapy, cirrhosis-related complications will also happen. In addition, patients with liver cirrhosis often have a poor liver function, which affects the implementation of radiotherapy and chemotherapy, and are prone to cause complications related to liver cirrhosis or radiotherapy and chemotherapy. Therefore, we hope you can agree with us. The authors stated

that the predominant cause of death during follow-up was not due to esophageal cancer or ESTD. Again, the authors should describe why the ESTD should be performed in these patients. If most of the esophageal cancer patients with cirrhosis will not die due to the esophageal cancer, there is less priority to perform ESTD in these patients. 10. This study is retrospective study, and the certain bias could not be excluded. For reaching conclusion that the esophageal ESTD can be safely and effectively performed in patients with liver cirrhosis, the comparison between ESTD and ESD in the cirrhotic patient's cohort should be performed. Please consider to discuss this point.

Answer: Dear professor, thanks for your suggestion. In our center, ESTD is a preferred endoscopic resection method for the treatment of early esophageal cancer; thus, we have little data on ESD for esophageal cancer patients with cirrhosis. Therefore, the comparison between ESTD and ESD in the cirrhotic patient's cohort cannot be performed in our study. The authors answered that the ESTD were preferred to perform in the author's affiliation. However, the comparison between ESTD and ESD is essential to evaluate the usefulness of ESTD. If the authors could not collect the ESD cases for early esophageal cancer with cirrhosis, this point should be described as limitation of the study in the discussion section.-----Please revise in the attached file "78391 Auto_edited" and reply within seven days, thank you!

Answer: Dear Editors and Reviewers, Thank you for your letter and for the reviewers' comments concerning our manuscript entitled "Endoscopic

submucosal tunnel dissection for early esophageal squamous cell carcinoma in patients with cirrhosis: a propensity score analysis” (Manuscript NO.78391).

We have addressed each comment raised by the reviewers and hope this revised manuscript is now acceptable. Each concern is discussed in detail below. We have revised the paper, and would like to re-submit it for your consideration. The amendments are indicated within the revised manuscript using track changes, as requested in the journal’s guidelines. Thank you for allowing us to resubmit our manuscript for your consideration. Sincerely,

Jin-Lin Yang Department of Gastroenterology and Hepatology, West China Hospital, Sichuan University, Chengdu 610041, Sichuan, China.

yangjinlin@wchscu.cn Reviewer #1: The manuscript has been revised well. I agree that the manuscript described the significance of ESTD for hepatic cirrhosis patients. I think this manuscript will be potentially acceptable after some correction have been done. I hope my comments would help to improve the quality of this article. 1. The authors stated that median overall survival (OS) could not be calculated because of the fewer deaths during follow-up period. However, the median OS estimation should be performed using Kaplan-Meier method and if less than 50% of the patients did not reach the endpoint, the authors should clearly state that point. Answer: Dear professor, thank you for your suggestion. We have described this point in the Survival outcomes and the Discussion section: During the study period, the number of deaths in the cirrhosis group and the noncirrhosis group was 8 and 4 patients,

respectively. Limited by the small number of deaths in both groups, the median OS could not be calculated. Since there were fewer deaths during follow-up in both groups, we were unable to calculate the median OS. Instead, the OS was used for long-term survival assessment. 2. The authors stated that the predominant cause of death during follow-up was not due to esophageal cancer or ESTD. Again, the authors should describe why the ESTD should be performed in these patients. If most of the esophageal cancer patients with cirrhosis will not die due to the esophageal cancer, there is less priority to perform ESTD in these patients. Answer: Dear professor, thank you for your suggestion. We have described this point and added two more references in the Discussion section as follows: It is also noteworthy that 7 out of 8 patients in the cirrhosis group died within 40 months after ESTD from complications of decompensated cirrhosis, including acute upper gastrointestinal bleeding and hepatic encephalopathy. Given these fatal complications, it is doubtful whether EESCC patients with comorbid cirrhosis should undergo ESTD. However, EESCC usually has a good prognosis after endoscopic resection, with a 5-year survival rate of more than 90% and a low incidence of complications [27]; thus, it is worth exerting effort for endoscopists to try it. In addition, based on current medical technology, it is difficult to predict which patients will survive longer and will really benefit from endoscopic surgery in the future [28]. Thirdly, cirrhotic patients are facing the need for further treatments to gain a better survival expectation in the future because their

untreated cancer may preclude them from undergoing liver transplantation. Therefore, endoscopic resection, such as ESTD, should be considered as an option for the treatment of superficial neoplasia of the esophagus [28].

Reference 27 and 28: 27 Berger A, Rahmi G, Perrod G, Pioche M, Canard JM, Cesbron-Métivier E, Boursier J, Samaha E, Vienne A, Lépilliez V, Cellier C. Long-term follow-up after endoscopic resection for superficial esophageal squamous cell carcinoma: a multicenter Western study. *Endoscopy* 2019; 51 :298-306 [PMID: 30261535 DOI: 10.1055/a-0732-5317] 28 Miaglia C, Guillaud O, Rivory J, Lépilliez V, Chambon-Augoyard C, Hervieu V, Ponchon T, Dumortier J, Pioche M. Safe and effective digestive endoscopic resection in patients with cirrhosis: a single-center experience. *Endoscopy* 2020; 52:276-284 [PMID: 31958860 DOI:10.1055/a-1089-9459]

3. The authors answered that the ESTD were preferred to perform in the author's affiliation. However, the comparison between ESTD and ESD is essential to evaluate the usefulness of ESTD. If the authors could not collect the ESD cases for early esophageal cancer with cirrhosis, this point should be described as limitation of the study in the discussion section.

Answer: Dear professor, thank you for your suggestion. We have described this point as limitation of the study in the Discussion section as follows: Finally, ESTD is a preferred endoscopic resection method for early esophageal cancer in our center; thus, we have fewer ESD cases of superficial esophageal carcinoma with cirrhosis. Therefore, the comparison between ESTD and ESD in the cirrhotic patient's cohort

cannot be performed in our study.