Dear Dr. Ma,

Thank you very much for your decision letter and advice on our manuscript (Manuscript NO.: 75463) entitled "*Optimal timing of biliary drainage based on the severity of acute cholangitis: A single-center retrospective cohort study.*" We also thank the reviewers for the constructive comments and suggestions. We have revised the manuscript accordingly, and all amendments are indicated in red font in the revised manuscript. Additionally, our point-by-point responses to the comments are listed below this letter.

We hope that our revised manuscript is now acceptable for publication in your journal and look forward to hearing from you soon.

With best wishes,
Yours sincerely,

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Firstly, we would like to express our sincere gratitude to the reviewers for their constructive and positive comments.

Replies to Reviewer 1

I read with interest the paper concerning optimal timing of biliary drainage in patients with acute cholangitis. I strongly believe there is a lack of knowledge in this particular topic and therefore the body of evidence gained is important. The contraindications of ERCP included acute coronary syndrome, acute heart failure (NYHA III-IV), stroke, and acute pulmonary embolism, while the contraindications of PTBD were platelet count less than 50,000/mm3 or prothrombin activity less than 60%. The second treatment included a second ERCP and a second PTBD for stone removal or stent placement. I agree with the authors that there are contra indications for ERCP as stated in the lines above, however the authors must clearly define what they mean with stroke and acute pulmonary embolism. Was it the anticoagulation that excluded the patients from ERCP? Was it the acute stroke or any form of medical history of stroke that excluded patients from adequate treatment?

Response: We appreciate your positive remarks on the present study and appreciate your interest in raising this critical issue. We have defined stroke as one occurring within 2 weeks prior to enrollment. In this study, acute pulmonary embolism was a contraindication of ERCP, because patients with acute pulmonary embolism were complicated with PaO_2 < 60 mmHg, which meant respiratory dysfunction. The definitions have been revised in the Methods section of the revised manuscript (Page 7, Lines 19-21).

Our primary outcome was IHM, and the secondary outcomes were hospital length of stay (LOS) and hospitalization costs. When analyzing the LOS and cost, we excluded patients who died or were transferred to other hospitals. I strongly believe if the authors exclude patients who died in their length of hospital stay and cost analyses there is a relevant selection bias. For sure as the authors stated correctly the LOS and the costs are higher in that group that survived, but this might contribute to the fact that those who did not get their biliary drainage timely with greater risk of dying and therefore the survivors for sure bedded a significant LOS and costs.

Response: We have revised the results of the LOS analysis and have provided additional details of the cost analyses of all the patients in the Results section (Page 10, Lines 2-5 , Table 1, Table 3) and revised the Methods section (Page 7, Lines 1-3) to present more details. The results were similar because most deaths occurred during the initial hospitalization period.

One hundred and sixty patients with Grade III were treated with antibiotics only (disagreement about

procedures = 35 cases; with contraindications = 24 cases; not tolerable conditions = 14 cases; obstruction spontaneous relief = 67 cases; not persistent biliary obstruction with high risk to stone removal by ERCP = 15 cases; not persistent biliary obstruction with selective cholecystectomy = 5). The authors must indicate what happened to those patients who did not underwent biliary drainage, how was the mortality rate in those patients?

Response: The total in-hospital mortality rates of Grade III patients, in whom biliary drainage was not performed, were 22/160 (Table 3). For each subgroup, the mortality was added in the Result section of the revised manuscript (Page 9, Lines 7-13).

Among the patients who underwent biliary drainage, 52.2% required a second intervention for stone removal or stent placement. Please indicate why these patients were treated in one single session? How many of them were treated outside regularly working hours? How good was the experience and expertise of the endoscopists who performed the intervention?

Response: The need for a second ERCP treatment was determined by the experienced endoscopists who administered the intervention based on the 2018 ERCP guidelines for China. Each of these endoscopists had independently completed 300 ERCP interventions per year for 3 years. In the revised manuscript, we have presented these details, and have included the number of patients who underwent drainage outside regular working hours (Page 7, Lines 24-27; Table 2).

Was there a difference between those patients graded severity 1 or 2 versus those graded severity grade 3 in the necessary of reintervention?

Response: This result has been added to Table 2 in the revised manuscript.

I wonder if the authors have dater about readmission of those who did not underwent biliary drainage, as this fact might significantly increase of the costs, and more over a 30- or 60-day mortality rate for sure would be of great interest! I believe looking at the singular hospital stay the mortality rate and the costs might be underestimated and therefore the importance of biliary drainage might be even higher having a closer look at that fact.

Response: We agree with the reviewer that it will be more credible to analyze relationships between drainage timing and readmission or 30- or 60-day mortality, and these factors have been considered in our ongoing prospective observational study; however, it would be difficult to follow-up with the patients to get more information in this retrospective study.

Replies to Reviewer 2

1. The abstract section can improve—add a focus point in the abstract section.

Response: Thank you for your thoughtful suggestion. We have added the focus point in the Abstract of revised manuscript (Page 3, Lines 3-8).

2. Rewrite the methods, results and conclusion (in the abstract) in a more straightforward form.

Response: The Methods, Results, and Conclusion sections of the Abstract have been revised (Line 15, Page 3 to Line 16, Page 4).

3. Currently, the severity grading criteria of AC from the Tokyo guidelines 2013 (TG13) are well accepted. No references?

Response: The introduction has been revised and this sentence has been deleted.

4. Objectives can be summarized into the introduction section.

Response: The objectives have been clearly presented in the Introduction section (Page 5, Lines 24-29).

5. Authors are suggested to use the full form when used for the first time throughout the manuscript.

Response: The full form has been added to the revised manuscript (Page 5, Line 17).

6. The introduction section is redundant. Authors can try to include the existing research limitations also, how the present research unravels those limits.

Response: The introduction section has been revised accordingly.

7. Aim of the study should need to add as the last paragraph in the introduction.

Response: Aim of the Study has been added as the last paragraph in the Introduction of the revised manuscript (Page 5, Lines 24-29).

8. Material and methods also look good. Need a logical flow of the writings with enough references and subtitles.

Response: The Material and Methods section has been revised accordingly (Line 2, Page 5 to Line 17, Page 8).

9. What was the exclusion criteria's?

Response: The exclusion criteria have been added to the Patients section of the revised manuscript

(Page 6, Lines 21-23).

10. All patients underwent obligatory colonoscopy for endoscopic verification of the diagnosis. Not clear.

Response: Endoscopy was not performed for all patients, whereas their diagnoses were based on the information present in the medical records, which met the diagnostic criteria of TG18 (Page 6, Lines 19-21).

11. Finally, 1305 patients were enrolled. How its calculated?

Response: Based on the pre-experimental results, which revealed a 0.87% and 3% mortality rates for patients who did and did not undergo biliary drainage, respectively, we calculated the sample size using PASS 15.0 with Power = 0.8, Alpha = 0.05, and N1=N2. The resultant sample size was 1306 (Page 6, Lines 10-14).

12. The results section can improve by adding significant results.

Response: All results have been mentioned with their corresponding significance values in the Results section of the revised manuscript (Lines 20, Page 8 to Line 5,Page 10).

13. The writing of results is good. Need to maintain a logical flow of the writings.

Response: The Results section has been revised to align with the improvements that you have asked for. We hope that the revised manuscript is suitable.

14. Figures presentation is not up to mark.

Response: We have revised the figures per your recommendations.

15. Figure legends are self-explanatory. Need to confirm without the repetition of the results and discussion in the figure legends.

Response: We have revised the Figure Legends to meet the requirements you have highlighted.

16. The discussion is good. The discussion section can improve by including the data from other sources about related works.

Response: We have improved the Discussion section of the revised manuscript per your recommendations, and have added the data from the previous research (Page 11, Lines 26-28; Page 13, Lines 24-28).

17. The conclusion needs to address future perspectives.

Response: We have added future research avenues and have mentioned our ongoing prospective study in the Conclusion of the revised manuscript to address this issue (Page 15, Lines 3-6).

18. Novelty of the work should be added by the author in the conclusion section.

Response: We have added some sentences in the Conclusion section of the revised manuscript to clarify the novelty of our research (Page 14, Lines 24-26).

19. Many spacing, punctuation marks problem found in the tables.

Response: The tables have been revised.

20. Spacing, punctuation marks, grammar, and spelling errors should be reviewed thoroughly. I found so many typos throughout the manuscript.

Response: The language, punctuation marks, and spacing have been revised thoroughly.

21. Consent to participate must need to include as supplementary.

Response: According to the ethics standard from General Office of the CPC Central Committee, the State Council General Office's "Deepening the Reform of the Examination and Approval system and Encouraging the Innovation of Drug (2017)," National Health and Family Planning Commission of the People's Republic of China's "Ethical Review of Biomedical Research Involving Human Projects (2016)," NMPA's "Good Clinical Practice of Pharmaceutical Products (2020)," WMA's "Declaration of Helsinki," and CIOMS's "International Ethical Guidelines for Biomedical Research Involving Human Subjects," after the review conducted by the Ethics Committee, the investigators received approval for the study protocol and the need for informed consent was waived. The certification has been submitted as supplementary material.

Replies to Reviewer 3

The paper is well written and the scientific quality is good. However, I think that the topic of the study has been discussed many times in literature. The need of an early decompression of the biliary tract in cholangitis is well known, as the timing, which should be as early as possible in severe patients. I think that you should move your study on less discussed matters and add it in your paper, which is still a good base. Best regards.

Response: We are thankful to the reviewers for these positive comments on our study and agree that

most experts accept the recommendations regarding the immediate need for patients to undergo biliary drainage in severe cases. However, most medical institutions in China are indeed unable to administer emergency endoscopic interventions outside working hours, and it remains controversial whether clinicians should transfer patients for drainage as early as possible, or whether the procedure should be delayed until stabilization has been achieved after adequate resuscitation, especially for Grade III AC patients. We consider it more meaningful to screen patients who would truly benefit from urgent drainage for hospital transfer that can reduce the risk of transfer and avoid the deterioration of the patients' condition, which prevents the wastage of medical resources.

Replies to Science editor

The authors conducted a single-center retrospective team to study the optimal timing of biliary drainage based on the severity of acute cholangitis. An interesting study. It is unacceptable to have more than 3 references from the same journal. To resolve this issue and move forward in the peer-review/publication process, please revise your reference list accordingly.

Response: Thank you for your positive comment and your decision on the present study. The references have been revised.

Signed Informed Consent Form(s) or Document(s) need to be supplemented.

Response: Since we conducted a retrospective review of patient data obtained from the electronic medical records of our hospital, and as stated by the ethical standards of China, the Ethics Committee exempted the need for obtaining informed consent. We have enclosed the certification as supplementary material.

The exclusion criteria need to be supplemented in detail.

Response: The exclusion criteria have been added in the Method section (Page 6, Lines 21-24) .

The article needs a great deal of language polishing.

Response: The language of the article has been polished by Editage.

Replies to Company editor-in-chief

I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Please authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content.

Response: We are grateful to the reviewers for your acceptance of our manuscript. We have revised the Tables as necessary to better present the requisite data.