Dear Editors,

On behalf of all the authors, I would like to thank you for your letter and for reviewers' comments concerning our manuscript entitled "Biliary disease caused by CMV infection in patients after liver transplantation: Extension of our previous knowledge" (Manuscript NO: 67955). Those comments are all valuable and very helpful for revising and improving our paper. We have carefully considered the reviewers' critical comments and insightful suggestions, responded to these comments and suggestions point-by-point, and revised the manuscript accordingly. In the revised manuscript, you will find the alterations that we made in response to the reviewers. All changes made to the text are underlined and highlighted so that they may be easily identified. In this response to reviewer letter, we also indicated how we have dealt with the reviewers' comments. Please find enclosed the edited manuscript in Word format (file name: Revised manuscript.docx)

Title: Biliary disease caused by CMV infection in patients after liver transplantation: Extension of our previous knowledge

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Name of Journal: World Journal of Clinical Cases

Manuscript NO: 67955

The manuscript has been improved according to the suggestions of reviewers and Editorial Office.

Comments:

Reviewer # 1

Comment 1: The authors do not analyze causality of biliary complications in patients after liver transplantation, neither in terms of presented data, nor in the choice of statistical methods and thus the title "Biliary disease caused by CMV infection in patients after liver transplantation: Extension of our previous knowledge" is inappropriate and requires modification.

Response: Thank you for your review and constructive comments. According to your comments, we have changed the title to" The impact of CMV infection on biliary disease after liver transplantation- Maybe an essential factor" (Page 1, lines 1-3).

Comment 2: Apart from liver failure ethology authors should provide details on liver transplantation urgency (chronic liver failure, acute liver failure, acute-on-chronic liver failure). Patients in these groups have different characteristics and different transplantation outcomes independently of CMV infection status.

Response: Thank you for your review and constructive comments. According to your comments, we have supplemented the details about LT urgency by PELD and MELD scores. We have compared MELD scores in adult patients between with and without complications. (Page 8, line 26-28; Table 1 and Table 2)

Comment 3: There are no details available on CMV prophylaxis after LT in material and methods section. A paragraph in discussion section suggests that patients were given ganciclovir or valganciclovir therapy only after CMV infection occurred.

Response: Thank you for your review and constructive comments. According to your comments, we have added the details about CMV prophylaxis after LT in the material and methods section（Page 5, lines 23-28）

Comment 4: Details concerning collection of bile specimen are well presented

however the time point after LT at which the procedure was performed is not stated (range, median or mean ±SD).

Response: Thank you for your review and constructive comments. We have added the time point that we obtained the bile from patients after LT (Page 8, lines 23-26).

Comment 5: Patients in group without biliary complications had bile specimens sampled during initial transplantation procedure and patients with complications had bile sampled after the complications occurred. If that is the case the whole comparison of patients seems pointless since CMV infection tends to occur within the first three months after transplantation and authors apparently compare patient infectious status at different time points.

Response: Thank you for your review and constructive comments. We agree that the comparison might be pointless that we compared the infectious status at different time points. We think it is necessary to clarify that the bile specimens from patients without biliary complications were obtained when the T-tube was removed, not during the initial surgery. The time points of removing T-tube were usually in three months after liver transplantation surgery. As the ambiguous expression, the sentences might cause misunderstandings, and we fix the sentences to make them more transparent. (Page 11, lines 10-13). But questions that the comparison might be pointless is remaining. It is inappropriate to place a long-term indwelling T-tube in a well-recovered patient. Patients with biliary complications had bile sampled after the complications occurred, compared to patients without complications, which is still in the different time points. The statistical results between patients with and without biliary complications might be meaningless. The result that all the patients without biliary complications had negative CMV-DNA in bile may provide the evidence for our conclusions.

Comment 6: There is no data available on known risk factors of biliary disease

in both groups such as: episodes of acute or chronic rejection. Allograft rejection can both damage bile ducts and trigger CMV reactivation after transplantation and thus it is important to report rejection episodes in both groups. There are no details available on hepatic artery thrombosis (HAT). Since HAT can cause ischemic injury of the biliary system and liver parenchyma leading to biliary necrosis it is essential to provide this data in the manuscript.

Response: Thank you for your review and constructive comments. We have added the data about risk factors associated with biliary complications, like graft rejection, HAT and surgical technique (Page 9, line 1-6; Table 1 and Table 2).

Comment 7: There is no data available on surgical anastomosis technique and perioperative risk factors. The factors that most commonly contribute to stricture formation include the surgical reconstruction technique (duct-to-duct anastomosis or choledochojejunostomy), cold ischemia time. There are also numerous scientific reports suggesting that a placement of a T-tube post-liver transplant is associated with a higher incidence of biliary complications (strictures, bile leaks, and cholangitis). Authors need to state in what extent T-tube was used in analyzed population.

Response: Thank you for your review and constructive comments. We have added the data about surgical techniques and information, like biliary reconstruction technique, cold/warm ischemia time and biliary drainage technique.(Page 9, line 1-6; Page 11, line 20-24; Table 1 and Table 2).

Comment 8: There are no p values presented for 2x2 tables (table 4 and 5) in the results section with authors using only % values.

Response: Thank you for your review and constructive comments. According to your comments, we have complemented the results and have discussed in the discussion. (Page 10, line 1 and line 13; Page 12, line 8-11; Page 13, line

2-4).

Reviewer # 2

Comment 1: It is not clear if all the patients that were transplanted in that period were enrolled in the study. If this is a retrospective study please clarify if bile samples for CMV are routinely collected.

Response: Thank you for your review and constructive comments. This is a retrospective study. We enrolled all the patients with biliary complications who underwent ENBD, PTCD, or indwelling T-tube for biliary drainage and all the patients without biliary complications who implanted T-tube during liver transplantation surgery from December 2012 to January 2020. For patients with complications, we routinely collected the bile samples every week by ENBD or PTCD. However, we could not routinely obtain the bile samples if the patients had no biliary complications. The bile samples from patients without biliary complications were obtained when the T-tube was removed. We added relevant content in the methods section (Page 6, lines 7-12).

Comment 2: Also, please describe the institutions routine For CMV detection and treatment. How about CMV prophylaxis?

Response: Thank you for your review and constructive comments. According to your comments, we have added the details about CMV detection and prophylaxis or preemptive therapy after LT in the material and methods section（Page 5, line 18-28）

Comment 3: What's the considered method for the diagnosis of biliary complications? Which complications were considered in this study?

Response: Thank you for your review and constructive comments. According to your comments, we have added the method for diagnosing biliary

complications in the methods section (Page 6, line 2-6) . The biliary complications were mainly referred to as biliary strictures (anastomotic and non-anastomotic), bile leaks and biliary stones, which had been defined in page 4, lines 18-20.

Comment 4: Results: not well structured. Tables are sometimes incomplete and some are pointless. 2 tables should be more then enough. Age in adults should not be expressed in months... Adults and children should not be mixed. Results should Be reported separately. Discussion: exclude the third paragraph (pointless)

Response: Thank you for your review and constructive comments. According to your comments, we have corrected and supplemented the results and made more discussions in the revised manuscript. We have changed the expression of age in adults into months in tables. Table 1 summarizes the patients' baseline, which included the data from children and adults, but in Table 2 we compared the baseline data in the adults' group to reduce the statistical error. Table 1 and Table 2 indicated the relevance between biliary CMV-DNA and biliary complications. In Table 3, patients with biliary complications were divided into two groups depending on age and then grouped according to biliary CMV status to explore factors related to it. We confirmed that the biliary anastomotic stricture was related to bile CMV infection in Table 4. CMV-DNA's positive rate in bile is much higher than that in blood in patients with biliary complications, the difference was not statistically significant in Table 5.

Science Editor:

1 Scientific quality: The manuscript describes a retrospective study to investigate the effects of CMV infection on biliary complications by comparing the levels of CMV-DNA in the bile and blood of patients after LT. The topic is within the scope of the WJG. (1) Classification: Grade D and

Grade D; (2) Summary of the Peer-Review Report: The paper addresses a very important topic of CMV infections in clinical practice in patients after liver transplantation. Current methods of diagnosing CMV infection have their limitations and thus authors must be praised for undertaking a research in that area. However the manuscript requires refinement in several aspects. (3) Format: There are 4 tables and 4 figures; (4) References: A total of 29 references are cited, including 1 reference published in the last 3 years; (5) Self-cited references: There are 0 self-cited references; (6) References recommendations: Please add more recente references 2 Language evaluation: Classification: Grade B and Grade B. A language editing certificate issued by MedE Editing service was provided. 3 Academic norms and rules: The authors provided the Biostatistics Review Certificate, the signed Conflict-of-Interest Disclosure Form and Copyright License Agreement, and the Institutional Review Board Approval Form. Written informed consent was also provided. No academic misconduct was found in the Google/Bing search. 4 Supplementary comments: This is not an invited manuscript. The study was supported by the National Natural Science Foundation of China (Grant No.81570586). The topic has not previously been published in the WJG.
Response: Thank you for the consideration of this paper and your comments. The questions raised by the reviewers have been answered point-by-point.

5 Issues raised: (1) PMID and DOI numbers are missing in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout;
Response: Thank you for the consideration of this paper and your comments. We have provided the PMID and DOI numbers in the reference list and list all authors of the references.

(8) The "Article Highlights" section is missing. Please add the "Article Highlights" section at the end of the main text;

Response: Thank you for the consideration of this paper and your comments. We have added the "Article Highlights" section at the end of the main text (Page 15, line 1-17).

6 Re-Review: Required 7 Recommendation: Conditional acceptance (after major review)

2 Company editor-in-chief: I recommend the manuscript to be published in the World Journal of Clinical Cases.

Response: Thank you for the consideration of this paper and your comments.

Finally, we wish to thank the Editors and the Reviewers for their valuable comments and suggestions that helped us to increase the value of our paper. We do hope that the revised manuscript is now acceptable for publication in *World Journal of Clinical Cases*.

Jing-Yi Liu.

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