

ROUND 1

December 28, 2020

RE: Manuscript NO: 61348 entitled "T-tube versus No T-tube in orthotopic liver transplantation for biliary tract reconstruction: An updated systematic review and meta-analysis"

Dear Editor:

Thank you very much for your email dated December 21, 2020, in which you informed us that our manuscript has been reviewed and invited us to revise and resubmit the manuscript for further consideration. We also thank you for including the critiques from the referees that were very useful for improving our manuscript. The comments, our point-by-point responses to them, and changes made in the manuscript are listed in separate pages.

We sincerely hope that the revised manuscript is now acceptable for publication in *World Journal of Gastroenterology*. If there are any further questions, please do not hesitate to contact us.

Sincerely yours,

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Responses to Reviewers' Comments

Reviewer #1:

"1. It was very nice to read this well-designed and well-performed meta-analysis."

Thanks.

"2. That using a T-tube increases the incidence of overall biliary complications, bile leaks and cholangitis significantly but did not reduce the incidence of postoperative biliary strictures since 2010 was an interesting and appealing conclusion of this study."

We thank the referee for the excellent summary of our work.

"3. However, the interpretations of the findings were not adequate or appropriate in the 'discussion'. So, I attached memos at some points in the manuscript. Please revise your interpretations so that readers can agree with you."

We greatly appreciate these suggestions. They were very useful for improving our manuscript. Our responses are listed below.

Sentence1: "the use of a T-tube prevents the scarring of the anastomosis parts of the biliary tract in biliary surgery"

Memorandum1: Please cite the evidence.

Repley1: The reference (PMID: 20517904) was added in the revised manuscript.

Sentence2: The inflammatory reaction and fibrosis processes may occur in the

points of biliary tract wall and the edges of the T-tube meet as a result of heterogeneity and mobility of a T-tube

Memorandum2: Please check the reference whether the context is correct.

It has been corrected in the revised manuscript. (PMID: 28754450, PMID: 8833487).

Sentence3: If a T-tube was placed on the biliary tract for a long time, the anastomosis parts of the biliary tract wall would be fragile and rigid due to a chronic inflammation.

Memorandum3: Please cite the evidence.

We have revised the sentences and added the reference (PMID: 7638576, PMID: 00005792-201904120-00037).

Sentence4: Maybe the development of medical concepts and technique dismissed the advantages of using a T-tube during OLT

Memorandum4: It is hard to understand this sentence.

We apologize for our vague expression. The sentence has been changed to "Although the recent advancement in surgical techniques has significantly improved the outcomes of the short-term graft after OLT (PMID: 30747842, PMID: 19898209). There are no significant differences in the incidence of biliary strictures after OLT between the two groups after 2010."

Sentence5: In any patients with shrunken gallbladder and biliary tracts, adhesion among biliary tracts and neighbor organs, or biliary anatomic anomaly, the probability of inappropriate place of T-tube increased, which then increased the risk of bile leaks or fistulas

Memorandum5: Do you believe this situation is relevant for patients undergoing OLT?

We agree with the referee that this situation is not relevant for patients

undergoing OLT. This sentence was deleted in the revised manuscript.

Sentence6: A T-tube was a bridge between abdominal cavity and external environment to facilitate entry of bacteria into human body. And the surface of a T-tube is a good platform for bacteria to implant so bacteria could form biofilm which help bacteria proliferate better. The biofilm in T-tube play an important role in occurrence of cholangitis.

Memorandum6: In the references, biofilms developed on indwelling medical devices such as central venous catheter. If you think biofilm in T tube plays an important role in the occurrence of cholangitis, please cite the references.

The reference (PMID: 8726310, PMID: 4073767) was added in the revised manuscript.

Sentence7: T-tube inserting also increased the risk of long-term biliary inflammation and biliary tract fibrosis.

Memorandum7: Please cite the evidence.

The reference (PMID: 00005792-201904120-00037) was added in the revised manuscript.

Sentence8: The modern diagnostic devices and the advanced endoscopic technique reveal a lot of latent complications (small thrombosis, local infections, mild internal hemorrhage and so on), which is difficult to be detected in the past.

Memorandum8: Do you think T-tube is associated with small thrombosis or mild internal hemorrhage that was difficult to detect in the past? Is it now diagnosed easily with the modern diagnostic devices?

Yes. We believe so.

Sentence9: There may be a potential bias because we only use English literature to seek studies.

Memorandum9: What else literatures do you think more suitable for this kind of study?

This sentence was deleted in the revised manuscript. Thanks.

Reviewer #2:

"This is an updated systematic review and meta-analysis of a surgical approach in liver transplantation to intent to solve a challenge question."

Thanks.

Reviewer #3:

"This systematic review and metanalysis aimed at evaluating the safety and effectiveness of T-tube placement after biliary reconstruction in the liver transplant setting. The Authors systematically reviewed the literature on the field, including 18 papers between 1995 and 2020. Furthermore, the studies were divided according to publication year (period 1: 1995-2010; period 2: 2011-2020). Metanalysis showed that no significant difference in terms of overall biliary complications or cholangitis were observed between groups in period 1, whereas T-tube placement seemed to be associated with biliary complication in studies performed between 2011-2020."

We thank the referee for summarizing our work.

"The study included only patients transplanted over 18 years of age. Therefore, this metanalysis refers only to adult LT. This should be added in the title of the manuscript."

The title has been changed accordingly. Thanks.

"Biliary strictures can be diagnosed also with MRI or CT scan, in patients without T-tube"

This information has been added in the revised manuscript.

"According to the Jadad score, the quality of studies, and their retrospective design, should be cited in the Discussion section, as potential pitfalls"

We thank the referee again for making this excellent suggestion. We have added the extra inherent limitations and study quality assessment to the "limitation section" of the Discussion.

"The Authors said that all studies were retrospective. However, the study by Lopez-Andujar was not a RCT, but a prospective, single center, study, which aimed at evaluating results of a previous RCT performed by the same Authors."

We thank the referee for pointing out this issue. The eight comparative studies were retrospective designs while the ten RCTs were prospective designs. The study performed by Lopez-Andujar et al. is prospective, randomized, blinded and set the control group and case group, which meet the criteria of the randomized controlled trials.

"The second paragraph of the discussion section, where the Authors dealt with the hypothetical role of T-tube on biliary strictures, is quite difficult to understand. I suggest to revise this section."

Reviewer #1 also had some similar comments. The discussion was revised accordingly. Please see our responses above. Thanks.

"Given the heterogeneity among studies and across results provided by this metanalysis, I suggest to modify the conclusion section in the Abstract body. Indeed, in my opinion, results are not strong enough to suggest against the use of T tube."

We thank the referee for the great advice again. The conclusion was changed to "there is no enough evidence to support the use of T-tube during OLT."

"English language polishing is needed. There are some typos throughout the manuscript (e.g., trail instead of trial; charcot instead of Charcot, systemic instead of systematic, did not reduce instead of did not reduced, "lost the significant")"

We apologize for the typographic errors. The manuscript has been corrected for proper English language, grammar, punctuation, spelling, and overall style by a fluent English speaker.

ROUND 2

February 23, 2021

RE: Manuscript NO: 61348 entitled "T-tube versus No T-tube in orthotopic liver transplantation for biliary tract reconstruction: An updated systematic review and meta-analysis"

Dear Editor:

Thank you very much for giving us another chance to revise our figures and tables. We also thank you for adding useful comments to improve our works. We upload the editable Figure 2-5, including A, B, arrows, content, etc. And the format of document was changed into "the surname + et al (italics) + references [number] (superscript)+ comma + Year". And we add the explanation to each Figure. We also add the bibliography of the study in the tables. For the second review report, our point-by-point responses to the two reviewers, and changes made in the manuscript are listed in separate pages.

We sincerely hope that the revised manuscript is now acceptable for publication in *World Journal of Gastroenterology*. If there are any further questions, please do not hesitate to contact us.

Sincerely yours,

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Responses to Reviewers' Comments

Reviewer #1:

1. *"I would like to thank for the opportunity to read the revised version of this manuscript. The Authors partly answered my previous comments."*

Thanks.

2. *"In detail: - there are still several typos, e.g., trail instead of trial; there are still redundant and very long sentences in the discussion section. Please carefully review the text before publication."*

We apologize for the typographic errors. We have recomposed the redundant sentences in the discussion section. And a fluent English speaker has carefully revised the text in grammar, punctuation, spelling, and overall style.

3. *"the manuscript Ref#26, PMID 30736977, is a prospective comparative study, which validated the results of a previous RCT performed by the same group (Ref#21, PMID 23426348). Therefore, I suppose there is still a mistake in table 1, where this study has been defined as RCT, as well as in related Figures. Moreover, the sentence dealing with the retrospective design of all comparative studies should be modified before publishing the paper. Since this manuscript has the potential to be highly cited, due its nature and the interesting topic in the setting of liver transplantation, I encourage the Authors to carefully check this point because methodology represents a strength of a metanalysis."*

We thank the referee for making this excellent suggestion. We have corrected the mistake in Table 1, and revised the relevant parts in the manuscript. We have corrected the description of the retrospective design of all comparative

studies. We also have excluded a study because it was the preliminary result of a RCT while the final result of the RCT was already included. And the related figures and tables have been corrected.

4. *"the Authors said that a minimum follow-up time for at least 3 months was an inclusion criterion, but they said that one study followed-up patients for 2 months. Please correct this sentence before publication."*

We apologize for this mistake. We have corrected the relevant sentences. Thanks.

5. *"I appreciate the revised conclusions in the abstract body. However, if we consider the relevant results of this metanalysis, it seemed that using T-tube was beneficial on biliary stricture before 2010, whereas no benefit was observed for overall biliary complication, biliary leak and cholangitis in the same period. Considering the studies after 2010, not using T tube was beneficial in terms of bile leakage and cholangitis, whereas (after sensitivity analysis), it was not associated with overall biliary complications and biliary strictures. Therefore, if we consider the conclusion of this metanalysis, we have to say that "studies published in the last decade did not provide enough evidence to support the routine use of T-tube in adults during OLT". Otherwise, a pooled analysis on ALL studies should be performed."*

We thank the referee for this suggestion. Accordingly, the conclusion was changed to "The studies published in the last decade did not provide enough evidence to support the routine use of T-tube in adults during OLT".

6. *"I would see data on heterogeneity in the result section in the abstract body."*

We have added the heterogeneous data in the result section in the abstract body accordingly. Thanks.

Reviewer #2:

“Please see the attachment”

We greatly appreciate these suggestions. They were very useful for improving our manuscript. Our responses are listed below.

Sentence1: T-tube vs No T-tube in adult orthotopic liver transplantation for biliary tract reconstruction: An updated systematic review and meta-analysis

Memorandum1: (1) versus; (2) no; (3) for biliary tract reconstruction in adult ... seems better.

Repley1: We thank the referee for this suggestion. Accordingly, we have revised the title of the manuscript.

Sentence2: We identified 18 studies (ten randomized control trials (RCTs) and eight comparative studies) from January, 1995 to October, 2020.

Memorandum2: controlled & the same below.

Repley2: We apologize for the typographic error. And we have corrected the mistake accordingly.

Sentence3: The data of the studies before and after 2010 were separately extracted. We chose the overall biliary complications, bile leaks or fistulas, biliary strictures (anastomotic or nonanastomotic) and cholangitis as outcomes.

Memorandum3: non-anastomotic

Repley3: We are sorry for this typographic problem. And we have corrected

the mistake accordingly.

Sentence4: This is the first meta-analysis that compared the postoperative outcomes of biliary tract reconstruction with or without biliary T-tube during OLT in the last decades and in the past decades.

Memorandum4: “in the last decades and in the past decades” need English polishing.

Repley4: We thank the referee for the brilliant suggestion. And we have corrected the sentences into “before and after 2010”, accordingly.

Sentence5: We identified the overall biliary complications, bile leaks or fistulas, biliary strictures and cholangitis as postoperative outcomes.

Memorandum5: So, what effects the T tube made on these outcomes? You need to describe it.

Repley5: We thank the referee for this suggestion again. We have added the description of the effect of the T-tube in revised manuscript accordingly.

Sentence6: Several randomized control trials and comparative studies have been conducted to evaluate the value of using a T-tube in biliary reconstruction during OLT.

Memorandum6: controlled. The same below.

Repley6: We apologize for the typographic error. And we have corrected the error accordingly.

Sentence7: Even meta-analyses on this issue have provided different suggestions,

Memorandum7: . period

Repley7: We have changed the “coma” into “period” accordingly. Thanks.

Sentence8: Sun Ning *et al.* indicated that the T-tube was an excellent tool for

biliary tract reconstruction while Sotiropoulos *et al.* suggested abandonment of t-tube was better.

Memorandum8: T-tube

Repley8: We apologize for the typographic error again. And we have corrected the error accordingly. Thank you very much.

Sentence9: Relevant comparative studies and randomized control trails (RCTs) in biliary tract reconstruction during OLT were identified.

Memorandum9: controlled. The same below.

Repley9: We have corrected the error accordingly. Thanks.

Sentence10: “trials with a follow-up at least 3 mo,”

Memorandum10: months

Repley10: We have used the word “months” in revised manuscript accordingly. Thanks.

Sentence11: “bile leaks or fistula, anastomotic or nonanastomotic strictures and cholangitis”

Memorandum11: non-anastomotic

Repley11: We apologize for the typographic error again. And we have corrected the error accordingly.

Sentence12: The following variables were considered: authors, year of publication, number of patients, sex, mean age of subjects and cold ischemia time (CIT) (min).

Memorandum12: Omit “(min)”, please.

Repley12: We thank the referee for this meaningful suggestion. And we have omitted “(min)” in revised manuscript accordingly.

Sentence13: “Right upper quadrant pain, jaundice, and fever”

Memorandum13: right

Repley14: We have corrected the error accordingly. Thanks a lot.

Sentence15: Outcome evaluated were: overall biliary complications, bile leaks or fistulas, biliary strictures, cholangitis. Odds ratios (ORs) with 95% confidence intervals (CI) were calculated to describe the results of dichotomous outcomes.

Memorandum15: (1) Outcomes; (2) “,” into “and”

Repley15: We apologize for the typographic error again. And we have revised the manuscript accordingly. Thanks.

Sentence16: Sensitivity analysis based on ten RCTs was used to test the stability of the results of all studies meta-analysis.

Memorandum16: “all studies meta-analysis” need English polishing.

Repley16: We thank the referee for this valuable suggestion. And we have changed the “all studies meta-analysis” into “all studies meta-analysis” accordingly.

Sentence17: Fourteen reviews, 5 case reports and 1 Letter were also excluded.

Memorandum17: letter

Repley17: We have revised the manuscript accordingly. Thanks.

Sentence18: Two studies were excluded because of the lack of no reference to patient selection or confounding variables or the use of T-tube in patients without a T-tube.

Memorandum18: a T-tube

Repley18: We apologize for the grammar error. And we have revised the manuscript accordingly. Thanks a lot.

Sentence19: The observation period was at least 3 mo except for one with

only 2 mo. In most studies, the T-tube was removed 3 mo after the biliary reconstruction operation, but in one comparative study, the T-tube was removed only 9 wk after operation.

Memorandum19: (1) months, the same below; (2) weeks

Repley19: We appreciate the valuable advice. And we have revised the manuscript accordingly.

Sentence20: The pooled results showed that in studies conducted between 1995 and 2010, the use of a T-tube appeared to reduce the incidence of biliary strictures

Memorandum20: results

Repley20: We are sorry for the grammar error. And we have revised the manuscript accordingly. Thanks.

Sentence21: Although, in the period from 1995 to 2010, the data showed that there was a trend that the use of a T-tube could reduce the incidence of biliary strictures and the use of T-tube had no influence on the occurrence of overall biliary complications, cholangitis and bile leak.

Memorandum21: a T-tube

Repley21: We have revised the manuscript accordingly. Thanks.

Sentence22: “we documented the use of a T-tube did not reduce the incidence of biliary strictures,”

Memorandum22: “,” into “and”

Repley22: We appreciate the useful suggestion. And we have changed the “,” into “and” accordingly.

Sentence23: Indeed, the use of a T-tube prevents the scarring of the anastomosis parts of the biliary tract in biliary surgery

Memorandum23: contradictory to the sentence of Memo [25]

Repley23: We apologize for this mistake. Accordingly, we have deleted the “the use of a T-tube prevents the scarring of the anastomosis parts of the biliary tract in biliary surgery”. Thanks.

Sentence24: However, unlike in most studies, there was no significant difference between the “with T-tube” group and the “without T-tube” group in the occurrence of biliary strictures in the period from 2010 to 2020 in our analysis.

Memorandum24: omit “in”, please.

Repley24: We have revised the manuscript accordingly. Thanks.

Sentence25: The inflammatory reaction and fibrosis processes may occur in the biliary tract wall that contacting with T-tube due to the foreign body reaction of a T-tube

Memorandum25: contradictory to the sentence of Memo [23]

Repley25: We have solved the question in Repley23. Thanks.

Sentence26: The recent advancement in surgical techniques has significantly improved the outcomes of the short-term graft after OLT

Memorandum26: short-term outcomes

Repley26: Thanks for the useful advice. Accordingly, we have revised the manuscript.

Sentence27: However, there are no significant differences in the incidence of biliary strictures after OLT between the two groups after 2010, which is proved by our updated statistic data.

Memorandum27: What relevance does this sentence have in this context?

Repley27: We thank the referee for this great advice. And we have deleted this sentence.

Sentence28: Nevertheless, we found that the use of a T-tube did increase the risk of developing bile leaks in biliary reconstruction during OLT in the period from 2010 to 2020.

Memorandum28: after OLT

Repley28: Accordingly, we have revised the manuscript. Thanks.

Sentence29: Previous studies show that 5% to 15% of patients suffer from Bile leaks after T-tube removal.

Memorandum29: (1) showed; (2) suffered; (3) bile

Repley29: We are sorry for these typographic problems. And we have corrected the mistakes accordingly. Thanks a lot.

Sentence30: Most patients were immunocompromised because of immunosuppressors after OLT, which made patients vulnerable to bacteria or viruses infection.

Memorandum30: bacterial or viral

Repley30: The sentence has been revised accordingly. Thanks.

Sentence31: In another words, it's fatal for some patients to suffer from infections such as cholangitis.

Memorandum31: suffering

Repley31: We have corrected the grammar error in revised manuscript. Thanks.

Sentence32: As for overall biliary complications, there was no significant difference the two groups in the period from 1995 to 2010, which suitable for old opinion that the use of a T-tube didn't increase the risk of overall biliary complications.

Memorandum32: between the

Repley32: We have corrected the sentence accordingly. Thanks.

Sentence33: Interestingly, our document showed that use of a T-tube did play a role in development of all kinds of biliary complications in the period from 2010 to 2020.

Memorandum33: the use

Repley33: Thanks for the useful suggestion. And we have revised the sentence accordingly.

Sentence34: The modern diagnostic devices and the advanced endoscopic technique reveal a lot of latent complications (small thrombosis, local infections, mild internal hemorrhage and so on), which is difficult to be detected in the past.

Memorandum34: (1) revealed; (2) was or would be

Repley34: We appreciate the meaningful suggestions. We have corrected the sentence in the revised manuscript.

Sentence35: We performed the meta-analysis to evaluate the whether the patient benefited from the use of the T-tube or not during OLT.

Memorandum35: (1) omit “the”; (2) omit “or not”; (3) a T-tube

Repley35: We thank the referee for the great suggestion again. Accordingly, we have corrected the sentence in the revised manuscript.

Sentence36: We calculated Odds ratios (ORs) with 95% confidence intervals (CI) to identify the role of the T-tube in the incidence of the overall biliary complications, bile leaks, cholangitis and the biliary strictures, protector or inducer.

Memorandum36: (1) odds; (2) a T-tube; (3) “protector or inducer” need grammar check

Repley36: Thanks. We revised the sentence accordingly.

Sentence37: However, in the recent decade (from 2010 to 2020), we found that T-tube didn't affect the occurrence of the biliary strictures and increased the incidence of the overall biliary complications, bile leaks, cholangitis.

Memorandum37: “,” into “and”

Repley37: Thanks for the useful suggestion. And we have revised the sentence accordingly.