

Dear Professor Lian-Sheng Ma,
President and Company Editor-in-Chief
Baishideng Publishing Group Co. Limited

Thank you very much for your response regarding our manuscript entitled "**Clinical problems with antithrombotic therapy for endoscopic submucosal dissection for gastric neoplasms**" We carefully examined the comments and revised the manuscript.

Point-by-point responses to the reviewers are attached for your convenience. We modified the manuscript using track changes mode in Word and we again asked a copy-editing company correct the syntax errors.

We sincerely hope that the revised manuscript is acceptable for publication in *World Journal of Gastrointestinal Endoscopy*.

All authors take responsibility for the content of the manuscript and satisfy the requirements for authorship.

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Sincerely,

Tsutomu Nishida

Responses to Reviewer 0007436's comments

Thank you very much for your valuable and constructive comments regarding our manuscript. We believe that your comments have significantly improved the revised manuscript.

Our responses to your comments are as follows:

- 1) If possible, the data about bleeding of endoscopic procedure (besides gastric ESD) under administrating DOACs should be revealed.

Our response

Thank you for this advice. Unfortunately, there has been no study of the effects of DOACs on endoscopic procedures. However, we agree that such studies are important. Therefore, we added the following sentence on Page 9, Line 14, in the revised manuscript:

Unfortunately, no study has examined the effect of DOACs on endoscopic procedures except our following conference paper.

- 2) I think that it is inappropriate to refer unpublished data in the table.

Our response

In accordance with your comment, we deleted the unpublished data in the table.

- 3) Please show the concrete “well-designed clinical studies” for the management of gastric ESD for the patients with antithrombotic therapy.

Our response

Thank you for this comment. We changed the phrase to “well-designed prospective and comparative clinical studies” in Page 14, Line 13, in the revised manuscript.

- 4) I think that English of this paper should be checked by the native speaker(s) of the expert gastroenterologist(s).

Our response

We have again asked a copy-editing company to correct the syntax errors

(American Journal Experts; <http://www.aje.com/jp/>).

Thank you very much. We believe that the revised manuscript is significantly improved because of your comments. We hope that the revised manuscript is acceptable for publication in *World Journal of Gastrointestinal Endoscopy*.

Responses to Reviewer 02954439's comments

Thank you very much for your valuable and constructive comments regarding our manuscript. We believe that your comments have significantly improved the revised manuscript.

Our responses to your comments are as follows:

The point of interest of this review was great; however, the reference related to the post-operative bleeding is not enough. This point is the biggest disadvantage.

Our response

Thank you for your constructive comment. We added a brief review of delayed bleeding after gastric ESD in the Introduction section on Page 4, Line 19.

Although antithrombotic drugs are closely related to the postoperative bleeding after gastric ESD, references to the periods of post-operative bleeding is required. Some of the previous report has divided the periods into the before and after 6 or 7 days. The authors showed HBT was high risk factor for post-bleeding. When was the periods, early or late phase? Please clarify.

Our response

Thank you for your constructive comment. We added a new paragraph about the timing of delayed bleeding on Page 10, Line 5.

Did the intervention such as second-look endoscopy to prevent post-operative bleeding have been described? Some other previous reports have been described. By these interventions, were there differences of respect to the risk factors or bleeding rate among the previous report?

Our response

Thank you for your helpful comment. As you mentioned, second-look endoscopy is frequently performed to prevent delayed bleeding. However, a recent analysis and recent randomized control study denied a preventive effect on delayed bleeding. We added sentences describing these results in the Introduction section on Page 5, Line 2.

Thank you very much. We believe that the revised manuscript is significantly improved because of your comments. We hope that the revised manuscript is acceptable for publication in *World Journal of Gastrointestinal Endoscopy*.

Responses to Reviewer 01468173's comments

Thank you very much for your valuable and constructive comments regarding our manuscript. We believe that your comments have significantly improved the revised manuscript.

Our responses to your comments are as follows:

1. The authors should present inclusion and exclusion criteria for the choice of the studies. It is not a systematic review, but at least some criteria for citation should be presented.

Our response

Thank you for this comment. As you know, it is difficult to perform a systematic review in this field because of the limited evidence and the variety of patients with various comorbidities receiving many types of antithrombotic drugs. Therefore, we prepared this manuscript as a narrative review, but we searched the entire MEDLINE database for studies on antithrombotic therapy and gastric ESD because the number of papers in this field is also limited. However, we also think such studies are very important. Therefore, we added the following sentence on Page 5, Line 17, in the revised manuscript; "This review is not a systematic review because of the limited evidence and the variety of patients with various comorbidities receiving many types of antithrombotic agents. However, we searched the entire MEDLINE database to identify the literature on antithrombotic therapy and gastric ESD and included as many studies as possible."

2. The author in this review, should be discussed what becomes clear and what is remains unclear.

Our response

Thank you for your constructive comment. As you advised, we added phrases on Page 8, Line 4, to clearly indicate the limitations of knowledge of conducting DAPT. In the section "Is HBT Feasible for Gastric ESD?" on page

11, Lines 9 and 16 in the revised manuscript, we explained that these data did not include gastric ESD cases and that evidence for gastric ESD is needed.

3. In part of Effect of Antiplatelet agents on gastric ESD, it was unclear that the frequency of delayed bleeding was significantly higher in patients receiving the single aspirin therapy or not compared with that in patients receiving DAPT with continuous aspirin and cessation of thienopyridines.

Our response

Thank you for your comment. However, we do not think that single aspirin therapy increases the risk of bleeding, regardless of temporary cessation or continuous use. By contrast, patients receiving DAPT have a significant risk of delayed bleeding. Therefore, we changed the sentences to make these points clear on Page 6, Line 23, in the revised manuscript.

4. Did the author get the evidence about the timing of ESD for early gastric cancer in the patients with coronary artery stents? If so, please let us show the data and paper.

Our response

Thank you for this comment. Unfortunately, we have no evidence about the timing of ESD and coronary stenting. There has been no study of delayed ESD after diagnosis of gastric cancer due to the use of antithrombotic therapy.

5. "We usually wait to perform ESD in patients with DES placement, ,," should be deleted.

Our response

We agree that this sentence is inappropriate. We changed the meaning of the sentence and change to "ESD can be delayed in patients with DES placement, provided that the EGC lesion is still considered resectable after the completion of required DAPT." in Page 7 Line 6.

6. In part of Effect of Anticoagulants on gastric ESD, the reference of 42 was

inappropriate for review.

Our response

Thank you for your comment. Unfortunately, there has been no study of the effect of DOACs on gastric ESD, but we agree that such studies are very important. Therefore, we added the following sentence on Page 9, Line 14, in the revised manuscript: “Unfortunately, no study has examined the effect of DOACs on endoscopic procedures except our following conference paper.”

7. In the part of Is HBT feasible for gastric ESD?, the author presented that ESD under continuous use of warfarin or switching warfarin to DOACs was one of options. However, is there any evidence about that? If no, the author should state there is no data.

Our response

Thank you for your comment. For clarity, we revised the sentence as follows: “continuous use of warfarin and switching warfarin to DOACs are candidate new strategies, although data to support their use are lacking” on Page 11, Line 15.

8. In part of The analysis of bleeding risk in ,,, the reference of 49 and unpublished data were inappropriate.

Our response

Thank you for your comment. However, we think this bleeding risk analysis is very important to answer clinical questions we face on in our daily work. Moreover, the risk factors differ in each analysis because many factors are related. Thus we think these data represent valuable results for the readers.

Thank you very much. We believe that the revised manuscript is significantly improved because of your comments. We hope that the revised manuscript is acceptable for publication in *World Journal of Gastrointestinal Endoscopy*.

Responses to Reviewer 01800545's comments

Thank you very much for your valuable and constructive comments regarding our manuscript. We believe that your comments have significantly improved the revised manuscript.

Our responses to your comments are as follows:

The authors demonstrated and reviewed the risk of bleeding in patients with antithrombotic therapy who underwent ESD for gastric tumors. But the details should be documented more closely, In heparin bridge therapy, the author showed Ref43 in NEJM, but I recommend the author to read it again. In this report, the number of endoscopic treatment was very small and only biopsy was performed in most cases. In addition the ways of HBT were different in each study. The authors should re-consider the meaning of HBT in gastric ESD.

Our response

Thank you for your helpful comment. We understand that Ref43 included mainly surgical cases and very limited cases of endoscopic procedure, and most of the endoscopic procedures were endoscopic biopsies. We also know that Ref44-46 did not include gastric ESD. However, these studies are valuable for gastric ESD and provided important directions for us. We agree that additional studies of gastric ESD are needed and sufficient evidence is lacking. We added sentences to explain this limitation and the need for further study in this field on Page 11, Lines 9-14.

In addition, the day of post-bleeding and thrombotic events are also important problems to manage patients. The authors should discuss it more.

Our response

Thank you for your constructive comment. We added a new paragraph about timing of delayed bleeding on Page 10, Line 5. As you suggested, the timing of thrombotic events is very important. Unfortunately, cases with thrombotic event were very rare (one or two cases in one paper), and there are no studies describing the timing of thrombotic events. We described the timing of thrombotic events in our case experience in this review.

Ref 42 and 47 were not suitable for review article.

Our response

Thank you for your comment. Unfortunately, there has been no study of the effect of DOACs on gastric ESD, although we think that such studies are very important. Therefore, we added the following sentence on Page 9, Line 14, in the revised manuscript: "Unfortunately, no study has examined the effect of DOACs on endoscopic procedures except our following conference paper."

We believe that the bleeding risk analysis described in ref 47 is very important to address clinical questions we face in our daily work. Moreover, risk factor differ in each analysis because many factors are related. Thus, we believe that these data represent a valuable result for readers because such analyses are rare in this field with limited evidence.

Thank you very much. We believe that the revised manuscript is significantly improved because of your comments. We hope that the revised manuscript is acceptable for publication in *World Journal of Gastrointestinal Endoscopy*.