April 3rd, 2023

Dear, Editor

In this time, we would like to submit our original paper entitled "**Assessment of delayed bleeding after endoscopic submucosal dissection of early-stage gastrointestinal tumors in patients receiving direct oral anticoagulants**" (**Number ID:** 03474116) for publication in your journal. This manuscript is new and has not been submitted to any other journals. We have attempted to address reviewers' comments and have revised the manuscript accordingly.

We think that this manuscript will be of a great interest to the readers of your Journal. All authors have read the manuscript and conflict of interest statement and approved their submission for publication.

We thank you for your consideration and prompt handling of our manuscript and look forward to hearing from you.

Sincerely yours,

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Our responses to comments raised by Reviewer #1

1. This is a very nice review focusing specifically on the issue of delayed GI bleeding after endoscopic submucosal dissection (ESD) for early-stage gastrointestinal tumors in patients receiving direct oral anticoagulant (DOAC) therapy. Based on the available evidence, the authors demonstrate that there is possibly a lot of mechanisms contributing to delayed bleeding after ESD and provide evidence-based data regarding the prevalence of bleeding in each location, types of anticoagulant use and their related complications after ESD, as well as pharmacokinetic and pharmacodynamic related delayed bleeding of DOAC. The authors propose that the key underlying factor responsible for the bleeding is probably due mainly to the effect of direct oral anticoagulant therapy. They also point out that the serum level of DOAC at trough is positively related to the prevalence of bleeding. They emphasize that there is currently no strong evidence to guide management in this setting leading to differences in practice guideline among the country. The authors call for incorporating pharmacologic parameters of DOAC such as plasma DOAC level at trough, and Tmax and anti-factor Xa activity into the current scoring system to stratifying risk of post-ESD delayed bleeding in each individual and encourage investigators to develop simple test for these pharmacologic parameters. I strongly agree with the authors and I think this review is worth to be published in terms of providing the beneficial information to the community and encouraging investigators to conduct the future research on the value of DOAC pharmacologic parameters on post-ESD GI bleeding.

   Response:
   Thank you for your comments. We also believe that this manuscript will be of a great interest to the readers of your Journal.

Our responses to comments raised by Reviewer #2

1. The progress of ESD and the post-bleeding are the issues of great concern, since that delayed bleeding after ESD for gastrointestinal tumors has been discussed in some previous works, these parts can be briefly described or focus on recent developments.
   Response:
   We agree with your suggestions. According to your suggestion, therefore, we summarized this part of "delayed bleeding after ESD for gastrointestinal tumors" and deleted about 400 words (abut 30%) in the revised version.

2. In section of Pharmacological characteristics of DOACs "Why should we monitor the anticoagulant effect of DOACs, this should be stated detailly. The clinical outcomes refer to the pharmacokinetic characteristics in special population or the genetic variations can be discussed.
   Response:
   Thank you for your comments. With agreement to your comments, we mentioned about "Why should we monitor the anticoagulant effect of DOACs" in the revised version, as below.

   P13: 4. Pharmacological characteristics of DOACs
   Although the pharmacodynamic parameters of DOACs differ significantly among individuals and anticoagulant effects also vary widely among patients receiving DOACs, the lack of approved methods to monitor the anticoagulant effect of DOACs makes it unclear whether the effect is adequate in patients receiving DOAC. Compared with vitamin K antagonist therapy (therapeutic international normalized ratio range: 2.0-3.0), a disadvantage of DOACs is that the dosage of DOAC cannot be controlled according to anticoagulant effect. Therefore, the trough and time to reach maximum plasma concentration (T_{max}) and anti-FXa activity of DOAC-metabolizing enzyme polymorphisms may be useful parameters for accurately monitoring the anti-coagulate effects of DOACs and selecting patients at higher risk of major bleeding. Developing a system that easily measures the anti–FXa activity and plasma level could be an important way to monitor the anticoagulant effect of DOACs in clinical practice.

3. In section 7 Gastrointestinal bleeding after ESD in patients receiving DOACs, the heparin-bridging therapy refers to DOACs with heparin-bridging or any anticoagulants with heparin-bridging?
   Response:
   I am sorry for the hard to understand expressions. We revised this part to understand clearly whether the heparin-bridging therapy refers to DOACs with heparin-bridging or any anticoagulants with heparin-bridging.

4. DOACs is current recommended for cancer patients due to phylaxis of Venous thrombosis, the balance between the major bleeding (especially for high risk in gastrointestinal tumors) and VTE could be discussed in summary.
   Response:

Thank you for your comments. With agreement to your comments, we added explanation about association cancer patients and VTE in patients receiving DOAC in the revised version, as below.

P20. 8 Future of ESD for patients receiving DOACs
DOACs is current recommended for not only patients with nonvalvular atrial fibrillation and venous thrombosis (VTE), but also patients with cancer due to prevention of VTE by clinical guidelines [86]. Treatment or prophylaxis of VTE for patients with cancer must always balance the risk of incidence or recurrent VTE with the increased risk of major bleeding and take into consideration the consequences of these outcomes (including mortality, financial cost, quality of life) [86]. Developing a system that easily measures the anti–FXa activity and plasma level could be an important way to monitor the anticoagulant effect of DOACs and may help physicians to treat DOAC patients receiving ESD, endoscopic treatment, and surgical treatment and with cancer in clinical practice.

5. As illustrated in section, there are subtle differences about the management of DOACs with ESD, the possible reasons could be discussed.
Response:
Thank you for your comments. We also believe that it is important to show the possible reasons for subtle differences about the management of DOACs with ESD among different guidelines. With agreement to your comments, we added comments in the revised version, as below.

P17. 6. Clinical guidelines: Management for patients taking DOACs in endoscopic procedures with higher risk for bleeding (ESD)
Thus, as summarized in Table 4, guidelines for the management of patients undergoing ESD for early-stage gastrointestinal tumors receiving DOACs differ among different countries. Although subtle differences about the management of DOACs with ESD is important in clinical practice, we consider to depend on the year in which the guideline was published, different dosing doses of DOAC in each country, different numbers of concomitant with antithrombotic drugs and different prevalence of genetic variations (e.g., CYP3A4/5, ABCG2, and ABCB1 polymorphism).

Our responses to comments raised by Editor in Chief

1. I have reviewed the Peer-Review Report, the full text of the manuscript, the relevant ethics documents, and the English Language Certificate, 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 provide decomposable Figures, organize them into a single PowerPoint file. Please check and confirm whether the figures are original. If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022. If an author of a submission is re-using a figure or figures published elsewhere, or that is copyrighted, the author must provide documentation that the previous publisher or copyright holder has given permission for the figure to be re-published; and correctly indicating the reference source and copyrights. For example, "Figure 1 Histopathological examination by hematoxylin-eosin staining (200 ×). A: Control group; B: Model group; C: Pioglitazone hydrochloride group; D: Chinese herbal medicine group. Citation: Yang JM, Sun Y, Wang M, Zhang XL, Zhang SJ, Gao YS, Chen L, Wu MY, Zhou L, Zhou YM, Wang Y, Zheng FJ, Li YH. Regulatory effect of a Chinese herbal medicine formula on non-alcoholic fatty liver disease. World J Gastroenterol 2019; 25(34): 5105-5119. Copyright ©The Author(s) 2019. Published by Baishideng Publishing Group Inc[6]". And please cite the reference source in the references list. If the author fails to properly cite the published or copyrighted picture(s) or table(s) as described above, he/she will be subject to withdrawal of the article from BPG publications and may even be held liable. 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/.

   Response:
   Thank you for your comments. We understand. We also believe that this manuscript will be of a great interest to the readers of your Journal.