Author's response to reviews

Title: The postoperative bleeding rate and its risk factors in patients on antithrombotic therapy who undergo gastric endoscopic submucosal dissection

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Author's response to reviews: see over
Dear Dr. Omae,

Thank you for reviewing our manuscript. We are pleased to note your favorable comment. We found your comments helpful and have revised the manuscript accordingly. Owing to your suitable advice, our manuscript became even better. We would like to comment about your opinion as below.

1. The author described that odds ratios of ESD duration is 1.04 (95%CI 1.10-1.08, p=0.025). However, there is no description of the reason that a long time of ESD duration is a risk factor for postoperative bleedings. For example, you spend more times to stop bleeding in Bleeding group than Non-bleeding group during ESD.

As you pointed out, we also consider that the tendency towards higher postoperative bleeding rates with longer ESD durations can be explained in terms of a longer time taken to achieve hemostasis while resecting the lesion. When multiple vessels require cautery, it follows that a number of vessels are present in the ulcer floor following ESD, and we can assume that this influences the postoperative bleeding rate. This sentence is in the part of discussion (see page 11).

2. In the Table2, are there significant differences in the lesion with ulcerative scars or not, histology, and standard or expanded indications?

In the bleeding group 5 patients had ulcerative scars, and in the non-bleeding group 16 patients had ulcerative scars. There was no significant difference between the two groups. There were 3 adenoma patients in the bleeding group and 9 adenoma patients in the Non-bleeding group. All the other patients had well-differentiated adenocarcinoma. Some
of the lesions were expanded indications, but there was no significant difference in the size of a lesion between the two groups. Moreover, no resected specimen showed SM invasion pathologically. We added this information in Table.2.

Minor
1. All patients who had postoperative bleeding were performed only EGD to stop bleedings. Are there patients who needed operation to stop bleeding?

No patient needed an operation to stop bleeding.
Dear Dr. Goto,

Thank you for reviewing our manuscript. We found your comments helpful and have revised the manuscript accordingly. Owing to your suitable advice, our manuscript became even better. We would like to comment about your opinion as below.

Major points

1. This study seems to be mainly aimed not to compare post-ESD bleeding rate between the A group and the non-antithrombotic (NA) group, but to elucidate the causal factors on post-ESD bleeding in the A group by comparing the bleeding patients to the non-bleeding patients. Accordingly, Table 2 and 3 would be more relevant than Table 1. To avoid the confusion, the authors should focus on the main purpose, and clearly describe the main aim in the Background section and the main outcome measure in the Methods section.

2. The abbreviated terms, “the A group” and “the NA group” are unnecessary. If the authors create groups in this study, the patients having antithrombotic agents should be divided into 2 groups, Bleeding group and Non-bleeding group.

Thank you for your advice. The rates of postoperative bleeding from post-ESD gastric ulcers following ESD for gastric tumors are unclear. So, firstly we would like to examine these rates in our institute. At the same time, we also wanted to investigate the risk factors for such bleeding. We have revised the manuscript accordingly (see page 3). “In this study, we examined the rates of postoperative bleeding from post-ESD gastric ulcers following ESD for gastric tumors in accordance with a protocol specifying uniform rules for cessation and recommencement of antithrombotic therapy, in a retrospective study. We also investigated the risk factors for such bleeding in a case-control study to provide effective prophylaxis.”
for such bleeding. Therefore, in table1, we think that it is necessary to compare Antithrombotic group with Non-antithrombotic group. Also, we have already classified Bleeding group as Non-bleeding group in the Antithrombotic group in Table2.

3. The study design should be clearly stated. If my interpretation is right, this should be a retrospective case-control study with consecutive data.

Thank you for your advice. We have revised the manuscript accordingly (see page 4).

4. In the multivariate analysis, PPI with gastroprotective agent was not a statistically-significant influential factor on post-ESD bleeding in the antithrombotic users (p = 0.054). Therefore, the authors cannot conclude that it is useful to prevent post-ESD bleeding.

Thank you for your advice. We have revised the manuscript accordingly.

The new title of this manuscript is “The postoperative bleeding rate and its risk factors in patients on antithrombotic therapy who undergo endoscopic submucosal dissection”.

And we changed expression as follows (see abstract conclusions section, page 10, page 12).

“In this study, although multivariate analysis did not show a significant difference (odds ratio: 0.27, p = 0.054) in combination therapy with a mucosal protective agent and a PPI, univariate analysis showed significant differences (p= 0.039) between the two groups. For the first time we added these results suggest that the addition of a mucosal protective agent may be effective in preventing post-ESD hemorrhage in patients on antithrombotic therapy.”

“On the contrary, a mucosal protective agent to PPI therapy, lowering the odds ratio for postoperative bleeding, which suggests that the addition of a mucosal protective agent might be effective in preventing post-ESD hemorrhage in patients on antithrombotic therapy. A further prospective study with a large sample will be needed to confirm these.”

5. Similarly, duration of ESD was a statistically-significant influential factor in the
analysis. The authors should mention it at least in the Discussion section.

Thank you for your advice. We revised the manuscript accordingly.
The tendency towards higher postoperative bleeding rates with longer ESD durations can be explained in terms of a longer time taken to achieve hemostasis while resecting the lesion. When multiple vessels require cautery, it follows that a number of vessels are present in the ulcer floor following ESD, and we can assume that this influences the postoperative bleeding rate. This sentence is in the part of discussion (see page 11).

6. Gastroprotective agent varies. The authors did not mention the details of gastroprotective agents which had been administered to the patients. It is overestimated to insist on its efficacy only by this study.

Thank you for your advice. We have added the details of the gastroprotective agents which were administered to the patients (see Page 6).
We have also revised the manuscript accordingly in various other places (see title, abstract, discussion section, conclusions section). And we changed expression as follows.
“In this study, although multivariate analysis did not show a significant difference (odds ratio: 0.27, p = 0.054) in combination therapy with a mucosal protective agent and a PPI, univariate analysis showed significant differences (p= 0.039) between the two groups. For the first time we added these results suggest that the addition of a mucosal protective agent may be effective in preventing post-ESD hemorrhage in patients on antithrombotic therapy.”

“On the contrary, a mucosal protective agent to PPI therapy, lowering the odds ratio for postoperative bleeding, which suggests that the addition of a mucosal protective agent might be effective in preventing post-ESD hemorrhage in patients on antithrombotic therapy. A further prospective study with a large sample will be needed to confirm these.”

7. I wonder why post-ESD bleeding within Day 2 was not taken into consideration in the analysis. The authors should make a comment of that reason.
Thank you for your advice. We performed EGD for all patients on Day 2, and no patient showed bleeding. These patients resumed taking antithrombotic agents on Day 3. Therefore, postoperative hemorrhage was defined as hematemesis and/or melena or a sudden drop in hemoglobin (Hb) $\geq 2$ mg/dL occurring after recommencing eating on Day 3, requiring an unscheduled EGD, at which bleeding was confirmed to be from the post-ESD ulcer. We have added this reason to the revised manuscript (see page 6).

Minor Essential Revisions
1. The number of references is inaccurate.

Thank you for your advice. We have corrected the number of references.