Author’s response to reviews

**Title:** Colorectal endoscopic mucosal resection with submucosal injection of epinephrine versus hypertonic saline in patients taking antithrombotic agents: propensity-score-matching analysis

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Responses to Reviewers
Osamu Goto (Reviewer 1): This is a retrospective, non-randomized comparative study regarding the safety and efficacy of injection solution in a single center, by using a propensity-score matching. The followings may be taken into consideration.

1. This is a comparative study, and the aim of this study is to compare the safety and efficacy of two injection solution in EMR. Therefore, the conclusion should be stated according to the aim, such as "two solutions were considered to be both safe and effective in colorectal EMR...."

   I appreciate the favorable comment raised by the reviewer. According to the comment, I have revised the text (Abstract: page 4 line 4-5; Discussion: page 14 line 15-18).

2. In the aim of abstract, the subjective should be limited to in cases with antithrombotic agents to avoid misleading the readers.

   I apologize for our confusion. Accordingly, I have added the sentence in the revised text (page 3 line 9).

3. The reason for the imbalance in operators of procedures between the groups will be briefly mentioned.

   I appreciate the appropriate comment of the reviewer. According to the comment, I have revised the limitation part of discussion (page 14 line 9-12, line 12).

Li-Chun Chang (Reviewer 2): Yamaguchi et al. conducted this retrospective study to compare the risk of bleeding between using epinephrine and hypertonic saline for submucosal injection. Their study disclosed that the risk of immediate bleeding and post-EMR bleeding was not different between injection with epinephrine and hypertonic saline in subjects with an antithrombotic agent. This is a well-written paper. Although a significant difference developed in many important variates between two groups, this was minimized by propensity score. However, the weakness is the prospective design. Too many confounders will influence the result even after adjustment. The followings are my comments:

1. Comorbidity has a massive impact on the risk of bleeding. A comprehensive evaluation of comorbidity, such as using Charlson comorbidity score, will minimize this confounder.

   I appreciate the valuable comment of the reviewer. According to the comment, I have added the Charlson comorbidity score in the Table 1 (Table 1, Methods: page 8 line 17-17, Results: page 10 line 9-10).

2. Is there any rule to decide which injection solution to use in the endoscopy unit? For neoplasm with a higher risk of bleeding, the endoscopists may prefer one epinephrine for submucosal injection. This may lead to bias.
I appreciate the appropriate comment raised by the reviewer. In the present study, injected solution was decided by the operated endoscopist as indicated in the method (page 7 last line). Whereas the trainee tended to select epinephrine-saline, the colonic polyp characteristics (size, location, and histological and macroscopic classifications) were not different in the tested two solutions as indicated in Table 3. The neoplasms characteristics might not be bias, and this explanation has been added to the limitation in the revised text (page 14 line 9-12, line 13).

3. I am curious about the reason why prophylactic clipping was performed in every EMR.

Thank you very much for the appropriate comment. When the present study was started, the efficacy of both prophylactic clipping and the solution selection for prevention of colorectal EMR related bleeding during antithrombotic therapy was not clearly demonstrated. Regarding the clipping, prophylactic clipping was selected during the present study. Evaluation of the efficacy of clipping might be further exploration, and please understand why we applied clipping for the colorectal EMR in the present study.