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Underwater versus conventional endoscopic mucosal resection for colorectal polyps



To the Editor:

We read with interest the article by Choi et al¹ making a comparison between underwater EMR (UEMR) and conventional EMR (CEMR) for colorectal polyps. The authors found that UEMR was a safe and efficacious alternative to CEMR. Because UEMR is an innovative technique, in our opinion, several questions deserve attention.

First, results from randomized controlled trials were inappropriately pooled with results from retrospective cohort studies. This goes against the precept of pooling studies with similar designs, populations, interventions, controls, and outcomes in the analysis. It is appropriate to pooled analysis based on the study design (subgroup). Moreover, the included studies by Hamerski et al² and Liverant et al³ were abstracts according to the references, and the information is not enough to be evaluated for the quality of the literature, as the author mentioned.

Second, for certain pooled results (recurrence rate, resection time), the data for analysis are relatively small, which makes the conclusion unstable. Moreover, owing to the heterogeneity, the shorter time for UEMR is less significant.

Third, according to the inclusion criteria, 2 important references were overlooked and were not included in the analysis.^{4,5} Because the data for comparison between UEMR and CEMR are limited, it is crucial to collect the related data so as to be as comprehensive as possible.

In conclusion, although the initial result shows that UEMR is a safe and efficacious alternative to CEMR, more evidence is still needed to enable a solid conclusion.

DISCLOSURE

Supported by National Science Foundation of China, Grant/Award 81902383; The Doctoral Scientific Research Startup Foundation of Liaoning Province, Grant/Award 2019-BS-146; Revitalizing Liaoning Talents Program, Grant/Award XLYC1907004; Young and Middle-aged Scientific and Technological Innovation Talent Support Plan of Shenyang City, Grant/Award RC200223. All authors disclosed no financial relationships.

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REFERENCES

1. Choi AY, Moosvi ZM, Shah S, et al. Underwater versus conventional EMR for colorectal polyps: systematic review and meta-analysis. *Gastrointest Endosc* 2021;93:378-89.
2. Hamerski C, Samarasena J, Lee DP, et al. Underwater versus conventional endoscopic mucosal resection for the treatment of colorectal laterally spreading tumors: results from an international, multicenter, randomized controlled trial. *Am J Gastroenterol* 2019;114:575.
3. Liverant ML, Yip B, Kwak N, et al. Su1690 Underwater endoscopic mucosal resection (EMR) shows a higher single session curative resection rate than conventional EMR technique: a single center experience [abstract]. *Gastrointest Endosc* 2016;83:AB397.
4. Cadoni S, Liggi M, Gallittu P, et al. Underwater endoscopic colorectal polyp resection: feasibility in everyday clinical practice. *United European Gastroenterology J* 2018;6:454-62.
5. Kim HG, Thosani N, Banerjee S, et al. Underwater endoscopic mucosal resection for recurrences after previous piecemeal resection of colorectal polyps (with video). *Gastrointest Endosc* 2014;80:1094-102. <https://doi.org/10.1016/j.gie.2020.11.008>

A “double-hit” damage mechanism can explain self-limited GI bleeding in COVID-19 pneumonia



To the Editor:

We read with interest the recent article by Cavaliere et al¹ regarding the conservative management of upper GI bleeding in patients who have COVID-19 pneumonia.¹ The authors concluded that lack of response to conservative therapy in 24 hours may indicate a need for GI endoscopy. Accordingly, we would like to find out the main reasons for these findings and identify possible “double-hit” (direct and indirect) damage.

Our suggestions come from various case series about upper and lower GI bleeding treated by conservative therapy with the use of proton pump inhibitors, blood transfusion, and supportive therapy with complete clinical recovery.^{2,3} Endoscopy was not always performed, so causes of the bleeding were not identified with certainty.

When endoscopy for upper GI bleeding was performed, peptic lesions with a low risk of rebleeding, such as acute

esophagitis, gastritis, gastroduodenitis, or Forrest's type III ulcers were mostly found.¹⁻³ Usually, these kinds of lesions do not require endoscopic hemostasis.⁴ With regard to the interaction between SARS-CoV-2 and the digestive system, it is known that this virus can bind and affect the cells of the GI system through angiotensin converting enzyme 2 and transmembrane serine protease 2, which are expressed on the enterocyte membrane and can therefore generate organ damage through the establishment of a prothrombotic state.⁵

Thus, the cause of GI bleeding can be related to both primary and secondary mechanisms.

On one hand, direct injury of the GI mucosa due to viral infection generates active mucosal inflammation sustained by an associated systemic cytokine storm. On the other hand, indirect damage from tissue hypoxia, coagulopathy, and acute illness-related stress worsens the pathologic changes in the mucous membrane of the whole digestive system.^{5,6} This can explain the clinical finding of self-limited bleeding that does not need hemostasis during endoscopy.

GI bleeding seems to be part of the COVID-19 presentation as it responds to systemic therapy (as other signs and symptoms), including anticoagulation therapy with low-molecular-weight heparin. In this report, multivariate analysis to determine potential predictors of upper and lower GI bleeding in COVID-19 patients confirmed that anticoagulants did not statistically increase this risk.⁷

This "double-hit" damage explains the decreased need for urgent endoscopy in COVID-19 patients with GI bleeding; however, it remains a challenging topic because of the complexity of this multiorgan systemic disease and its related therapy. Many other risk factors (associated antiplatelet therapy, administration of steroids, history of GI bleeding) must be taken into consideration to tailor the endoscopic approach.

DISCLOSURE

All authors disclosed no financial relationships.

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REFERENCES

1. Cavaliere K, Levine C, Wander P, et al. Management of upper GI bleeding in patients with COVID-19 pneumonia. *Gastrointest Endosc* 2020;92:454-5.
2. Mauro A, De Grazia F, Lenti MV, et al. Upper gastrointestinal bleeding in COVID-19 inpatients: incidence and management in a multicenter experience from northern Italy. *Clin Res Hepatol Gastroenterol*. Epub 2020 Aug 14.
3. Melazzini F, Lenti MV, Mauro A, et al. Peptic ulcer disease as a common cause of bleeding in patients with coronavirus disease 2019. *Am J Gastroenterol* 2020;115:1139-40.
4. ASGE Standards of Practice Committee; Banerjee S, Cash BD, Dominitz JA, et al. The role of endoscopy in the management of patients with peptic ulcer disease. *Gastrointest Endosc* 2010;71:663-8.
5. Almeida Vargas A, Valentí V, Sánchez Justicia C, et al. Severe colon ischemia in patients with severe coronavirus-19 (COVID-19). *Rev Esp Enferm Dig* 2020;112:784-7.
6. Monkemüller K, Fry L, Rickes S. Covid-19, coronavirus, SARS-CoV-2 and the small bowel. *Rev Esp Enferm Dig* 2020;112:383-38.
7. Martin TA, Wan DW, Hajifathalian K. Gastrointestinal bleeding in patients with coronavirus disease 2019: a matched case-control study. *Am J Gastroenterol* 2020;115:1609-16. <https://doi.org/10.1016/j.gie.2020.12.022>

Response:



We thank Dioscoridi et al¹ for their interest in our letter.² In our letter, we presented a conservative approach to the management of GI bleeding in 6 patients with coronavirus disease 2019 (COVID-19) early in the pandemic. Dioscoridi et al² discuss that GI bleeding in COVID-19 is self-limited because of a 2-hit mechanism.

To understand whether this mechanism is plausible, it is important to identify the causes of GI bleeding. Unfortunately, as the authors state, the majority of COVID-19 patients with GI bleeding do not undergo endoscopy and have self-limited bleeding.²⁻⁴ We recently expanded on our initial case series and described the risk factors and outcomes in 314 COVID-19 patients with GI bleeding during the pandemic.⁵ Of the 314 patients (point prevalence of 3%), only 6% underwent endoscopy. Of the patients who underwent endoscopy, 55% had gastroduodenal ulcers, and the rest had lesions such as esophagitis, gastritis, colitis. We found that anticoagulation was not a risk factor for GI bleeding, similarly as in the study by Martin et al.³

It is likely that COVID-19-induced coagulopathy does play a role in GI bleeding. This would explain the endoscopy findings of bleeding esophagitis, gastritis, duodenitis, and colitis seen in these patients.³⁻⁶ It would also explain why the dosing of anticoagulants does not appear to increase the risk of GI bleeding in these patients^{3,5} and showed a mortality benefit in retrospective studies.^{7,8}

In conclusion, the mechanism for GI bleeding in COVID-19 does appear complex. We agree with Dioscoridi et al¹ that a 2-hit mechanism is possible. However, the lack of complete endoscopic data from COVID-19 GI bleeders,