

Revision letter

Dear Editor,

We recently received responses from the editors and reviewers to our manuscript entitled 'Role of endoscopy in acute gastrointestinal bleeding in real clinical practice: An evidence-based review' that we submitted to *World Journal of Gastrointestinal Endoscopy*.

We greatly appreciated the opportunity to revise the paper. We have revised it carefully in response to the comments of the editors and reviewers and provide a point by point account of the changes made below. And we attached figure file as a PPT format.

We thank you for the excellent comments and suggestions, and hope the enclosed revised manuscript is now found to be suitable for publication.

Thank you in advance

Sincerely,

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Reviewer #1:

It is a great pleasure for me to review your interesting study. I was very impressed with your achievements. Therefore, I think this paper is worth accepting publication.

Response: We appreciate the favorable comments and the result of the evaluation of the reviewer.

Reviewer #2:

In this manuscript authors reviewed the role of endoscopy in the acute GI bleeding. We appreciate authors effort for writing such detail review and pointing out the important aspects of endoscopy in the acute GI bleeding in clinical practice. I have some comments to authors.

1) There is no comment on small bowel bleeding. Should it be considered differently? As the title is the role of endoscopy on acute GI bleeding, would you like to comment on small bowel bleeding and the role of enteroscopy in the acute GI bleeding?

Response: We thank the reviewer for pointing this out. In response, the sentence in last part of diagnosis section on page 12 was added like below. In particular, we mentioned that part of small bowel bleeding was limited described in this review.

Approach to Unknown Gastrointestinal Bleeding

Obscure GI bleeding (OGIB) is defined as persistent or recurrent bleeding, despite of examination by esophagogastroduodenoscopy or colonoscopy. OGIB can be divided into overt bleeding with apparent gastrointestinal hemorrhage, such as hematochezia or melena, and occult bleeding, with repeated positive findings of fecal occult blood test or laboratory finding of iron deficiency anemia. This OGIB accounts for about 5% of all gastrointestinal bleeding, and it is known that more than 80% of these bleeding occur in the small intestine. The development of capsule endoscopy has enabled the full examination of small intestine mucosa. The device-assisted enteroscopy has enabled therapeutic endoscopy for these lesions. Details of small bowel bleeding are not covered in this review, but only the common causes of small bowel bleeding are summarized in the table 2.

2) What are the pre-requisites for the emergency endoscopy in acute GI bleeding. Do you recommend placement of nasogastric tube, use of prokinetic (motility) drug and which drug?

Response: We thank the reviewer for pointing this out. In response, the sentence before therapeutic part on page 15-16 was added like below.

The initial treatment of patients with GI bleeding is to restore the stability of the hemodynamic circulation. In order to maintain blood vessel volume and hemodynamic stability, it is important to secure a large vein, and it is important to check whether it is accompanied by heart, kidney, and liver disease

Although the nasogastric tube insertion is controversial, it can detect the need for immediate endoscopic hemostasis if blood is seen from the upper gastrointestinal hemorrhage to the nasogastric tube. However, it should be remembered that there may be a false negative due to duodenal hemorrhage. One dose of antibiotic erythromycin administered 30-120 minutes before endoscopy is not recommended on a routine basis, but it is recommended to improve endoscopic visualization, reduce the need for transfusion and endoscopy, and reduce the length of hospital stay.

3) Kindly enlist the causes of acute upper GI bleeding (like LGIB)

Response: We thank the reviewer for pointing this out. In response, we made a table for upper GI bleeding like below.

Table 1. Causes of upper gastrointestinal bleeding

Common causes	Other causes
Peptic ulcer disease (gastric or duodenal)	Hemosuccus pancreaticus
Gastric or esophageal varices	Cameron lesions
Erosive esophagitis	Hemobilia
Upper gastrointestinal tumors	Aortoenteric fistula
Upper gastrointestinal angioectasias	Anastomotic bleeding
Mallory-Weiss tear	Arteriovenous malformation
Gastric or duodenal erosions	Acute esophageal necrosis
Dieulafoy lesion	Atrial-esophageal fistula
	Gastric antral vascular ectasia

4) Please mention regarding Rockall score for peptic ulcer bleeding as it considers pre and post endoscopic finding and helps in predicting the risk of rebleeding and mortality

Response: We thank the reviewer for pointing this out. In response, the sentence before therapeutic part on page 14-15 was added like below.

Risk stratification and pre-endoscopic assessment for gastrointestinal bleeding

In patients with suspected upper gastrointestinal bleeding including hematemesis or melena, treatment may be different according to the etiology of the bleeding. However, the evaluation of vital signs, hemodynamic status and appropriate fluid treatment are important in all patients. If there are hypovolemic shock, rapid pulse rate, high blood urea nitrogen level, decreased urine volume at the time of presentation or previous history of acute bleeding, more aggressive initial monitoring, fluid treatment, and blood transfusion treatment are needed. However, if there is suspicion of massive bleeding, careful observation and follow up are necessary because early level of hemoglobin in acute bleeding may be normal.

The scoring system used when referring to the emergency department due to upper gastrointestinal bleeding can be divided into two types, one that includes endoscopic findings and the other that does not. The most commonly used scoring system is the Rockall score (RS) published by Rockall et al. In 1996. This scoring system predicts the likelihood of death within 30 days by using the five factors: patient age, accompanying shock, co-morbidities such as heart, liver, and kidney, causative diseases of bleeding, and endoscopic bleeding stigmata. However, since there is a disadvantage that the endoscopic findings must be known, in practice, the preendoscopic RS that can be calculated with the three findings except the etiology of the bleeding and endoscopic findings is used. This is useful for predicting rebleeding and mortality risk.

In addition, the Glasgow-Blatchford score (GBS) developed in 1882, which was calculated from patient's symptoms, blood test, physical examination, and accompanying diseases before endoscopy, is widely used to predict the need for transfusion, endoscopic treatment, rebleeding rate and prognosis. In particular, this scoring system has the advantage of being able to quickly and simply measure in the emergency room due to blood urea, hemoglobin, systolic blood pressure, pulse rate, presence of melena or syncope, liver disease, and heart failure.

Recently, AIMS65, a simpler scoring system, has also been proposed, including albumin, prothrombin time, mental state, systolic blood pressure. It is easy to memorize, and it can be calculated objectively and easily. In one study, mortality from AIMS65 scores ranged from 0.3% to 32%.

5) Under the heading what is the best option for patients with hematochezia .. first sentence -unlike UGIB which is mostly divided into variceal bleeding and peptic ulcer bleeding...replace peptic ulcer word by non-variceal.

Response: We thank for recognizing small important points. This was done. Please see new version of the manuscript. Changes are highlighted in **yellow**.

6) Kindly change the title use of endoscopy in therapeutic role to therapeutic role of endoscopy.

Response: We thank for recognizing small important points. This was done. Please see new version of the manuscript. Changes are highlighted in **yellow**

In this session, it would be useful to discuss endoscopic treatment in detail including some information about hemospray, over the scope clip with their indication and adverse events. Please comment on the challenges faced during endotherapy in patients with acute GI bleeding.

Response: We thank the reviewer for pointing this out. In response, the sentence on last of therapeutic part on page 25 was added like below.

5) Recent developments for endotherapy in patients with acute GI bleeding

Various endoscopic therapies have been attempted in cases of failure of hemostasis due to general endoscopic treatment. The OTSC (Over-the-scope clip, Ovesco AG, Tübingen, Germany) system, which is inserted at the upper end of the endoscope, has been widely used in fistulas and perforations. However, it can be used in cases of continuous hemorrhage due to local injection or clipping. In addition, the hemostasis of the bleeding site through the nano powder (Hemospray, Cook Medical, Winston-Salem, NC, USA) or starch (EndoClot Plus Inc., Santa Clara, CA, USA) can be used when other hemostasis is not treated. Previously, it was difficult to distribute the powder or starch materials to the hemorrhagic lesion, but in recent years, disposable powder roots have been developed and can be used more easily.

7) In peptic ulcer bleeding (under use of endoscopy in a therapeutic role) please add the sentence "risk of rebleeding associated with FIB is very less compared FII A and F IIB and may not require high dose IV PPI after successful endotherapy. (reference Jensen D M et al Reassessment of Rebleeding Risk of Forrest IB (Oozing) Peptic Ulcer Bleeding in a Large International Randomized Trial. Am J Gastrpenterol 2017 Mar;112(3): 441-446)

Response: We thank the reviewer for pointing this out. In response, the sentence on last of therapeutic part on page 19 was added like below.

After endoscopic treatment for spurting bleeding or exposed vessel lesion, which is known to be

highly rebleeding, high dose PPI is known to be an important medication to prevent rebleeding. However, according to recent study, risk of rebleeding associated with Forrest Ib is very less compared Forrest IIa and IIb and may not require high dose IV PPI after successful endotherapy.

8) What is your opinion on the use of video capsule endoscopy in critically ill patient? As these patients are at high risk of complication during endoscopic evaluation, can video capsule endoscopy be preferred for triage before evaluation?

Response: Thank you for your question. If we have a specialist who can interpret the capsule endoscopy in the emergency room and we have a system that can be operated for 24 hours, it would be useful to do capsule endoscopy in a triage. However, there is a limit to apply in general hospital systems.

9) I agree with the author second look endoscopy is not required for all the patient, but there is subset of patient who may benefit from second look endoscopy like patients on NSAID, those who required large amounts of blood transfusion and initial unsatisfactory endoscopic procedure. (ref Park SJ et al Effect of scheduled second-look endoscopy on peptic ulcer bleeding: a prospective randomized multicenter trial. Gastrointest endoscopy 2018 Feb;87(2) :457-465)

Response: We thank the reviewer for pointing this out. In response, the sentence on last of second look endoscopy part on page 31 was added like below.

However, a recent multicenter prospective study showed that the success of initial hemostasis, the use of NSAIDs, and the large number of blood transfusions were independent risk factors for rebleeding. Therefore, scheduled second-look endoscopy could be helpful for patient with unsatisfactory initial endoscopic hemostasis, use of NSAIDs, large amounts of blood transfusions.

10) Conclusion- conclusion is too big. Kindly avoid the same sentence repeatedly. It would be great if conclusion can be made shorter and precise.

Response: We appreciate the very important comment. As the reviewer has mentioned, we changed the [subject to conclusions and revised manuscript like below](#).

Conclusions

The symptoms of bleeding in the GI tract that are encountered in real clinical practice are mainly

melena, hematemesis, and hematochezia. When a patient with these symptoms presents to the emergency room, endoscopic diagnosis and treatment are considered together with appropriate initial resuscitation. For better prognosis in cases of suspected variceal bleeding, it is paramount that endoscopy is performed immediately after the patient is stabilized, and it would be sufficiently effective for endoscopy to be undertaken within 24 hours from symptom development for non-variceal UGIB. In cases of suspected LGIB, sigmoidoscopy may be initially performed if there is a strong suspicion of anorectal bleeding. However, on the whole, full colonoscopy after bowel preparation is effective for distinguishing the cause and location of bleeding and treating with hemostasis.

There are three methods used to perform hemostasis by endoscopy: injection, thermal, and mechanical therapy. Using a mechanical method or injection therapy combined with other modalities, rather than injection therapy alone, increases the success rate of bleeding control. In patients in the ICU, bedside endoscopy may be effective, but prophylactic intubation is still controversial. Proper endoscopic hemostasis can affect prognosis and prevent rebleeding. Routine second-look endoscopy does not affect the outcome of hemostasis, but it may be helpful in selected patients with a high risk of rebleeding. From the emergency room to discharge of the patient, the contents of this review are summarized in Figure 1.

In conclusion, the role of endoscopy in GIB is very important, and many guidelines have been developed about endoscopic treatment for specific bleeding diseases. However, there are still parts that have not been established. Especially, further studies on prophylactic intubated endoscopy, routine second-look endoscopy and emergency capsule endoscopy issues are needed.

Thank you very much for the detailed review.