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Title: Prediction models for recurrence in patients with small bowel bleeding

Reviewer comments.

Reviewer 1. Specific Comments to Authors: Small intestinal hemorrhage is a clinically complex disease to examine and treat; further knowledge accumulation is desirable. This manuscript also provides information that will help in this regard, and the scoring system presented is essential. The REMITTE score, particularly, has a high AUC and may be helpful. However, this manuscript is a document that only lists information and needs more substance in its discussion. There will be much to consider regarding the different scoring systems used and comparisons regarding their details. There are also a few citations to reference in the Introduction, and the data on gastrointestinal bleeding, both upper and lower, need to be revised. The document needed to be more refined.

Answer: Thank you for your valuable comments and thorough evaluation. We have reviewed the manuscript and agree with your comment. Our initial article only listed and described existing prediction models. It lacked our own view of different risk factors, and comparison of different models. In this regard, we have extensively reviewed and revised the entire manuscript, added comments in discussion section, and added comparison of some risk factors.

We have added the following after introduction section:

RISK FACTORS FOR REBLEEDING

To date, there are conflicting results about re-bleeding rates and associated factors from different studies, as patients included in each study are heterogeneous and follow-up durations vary. Analysis on risk factors associated with rebleeding are also different among different studies. Some factors considered to be associated with

rebleeding include overt bleeding, anticoagulation therapy, positive CE findings at initial assessment, age, gender, low serum hemoglobin, and accompanying conditions, such as liver cirrhosis and chronic kidney disease[17].

CE findings

Findings from CE can be classified into three types according to Saurin classification; P0 Lesions such as submucosal veins, diverticula without bleeding, or nodules without mucosa breaks have no bleeding potential; P1 Lesions such as red spots, and erosions have uncertain bleeding potential; P2 Lesions such as large ulcers, tumors, varices, and vascular lesions have high potential for bleeding[24]. Lorenceau-Savale *et al*[25] reported that a year follow-up of patients with P0 or P1 Lesions showed no rebleeding, while a study by Koh *et al*[26] reported rebleeding in 23% of patients with P0 and P1 Lesions within 6 mo after the initial presentation, and a prospective study by Laine *et al*.[27] showed similar results, reporting rebleeding in 33% of patients with negative initial CE results. Yung *et al*[17] included 26 studies from eastern and western populations for meta-analysis on clinical outcome from small bowel bleeding with negative initial CE, and reported that pooled rate of rebleeding after negative CE was 0.19 which is significantly lower than positive CE of 0.29 ($P < 0.001$). In another meta–analysis by Tziatzios *et al*[19] they used 46 studies from different countries to analyze re-bleeding rates. Similar to previous studies, they also reported that rebleeding rate was lower in negative CE compared to positive CE (22% *vs*. 28%). However, when analysis was done separately for eastern and western population, similar findings were observed only in eastern population studies and not in western population studies[19].

Occult and overt bleeding

Studies comparing overt and occult bleeding also reported varying results. Study by Liu *et al*[28] reported that among 142 patients with OGIB, rebleeding was observed in 72 (50.7%) patients over 6 mo, and among them initial presentation was overt bleeding in 70.4% compared to 38.6% of occult bleeding. Another study by Wetwittayakhlang *et al*[29] reported that during follow-up duration of 26 mo 35 patients (26.3%) had rebleeding where 60% had initial presentation as overt bleeding, and study by Kim *et al*[30] reported that 16 patients (26.7%) with negative CE had rebleeding within 36 mo

and among them 81.3% had overt bleeding as initial presenting symptom. In a study by Baba *et al*[31] 168 patients with small bowel bleeding were included and patients were grouped according to overt ongoing bleeding, overt previous bleeding, and occult bleeding. Multivariate analysis on rebleeding showed that overt previous bleeding (Odds ratio 3.68, $P = 0.01$), together with vascular lesions and chronic kidney disease were risk factors associated with rebleeding. Other studies reported different results. Multicenter study by Kim *et al*[32] reported that no significant difference was observed between overt and occult bleeding in patients with rebleeding, and such findings were also reported by Magalhães *et al*[33]. Some studies reported that overt bleeding was not a significant risk factor in rebleeding[28, 30, 33], while different studies have reported that overt bleeding is a significant risk factor for rebleeding[29, 31, 34]. Meta-analysis on initial mode of OGIB presentation showed that difference was not statistically significant in re-bleeding after negative CE[17] and overall odds ratio did not differ between two modes of presentation[19].

Therapeutic intervention

Once bleeding lesions are identified, DAE can be used for endoscopic hemostasis such as argon plasma coagulation, or hemostatic clipping. Other specific treatment include surgical, angiographic hemostasis, discontinuation of anticoagulants and antiplatelets, and treatment targeted for specific lesions such as Crohn's disease. When bleeding lesion was not identified (negative CE), watchful waiting, blood transfusion, or iron supplementation are considered as nonspecific treatment. Some studies concluded that receiving targeted therapeutic intervention did not have significant effect on rebleeding[32, 35], while other studies reported that targeted specific therapeutic intervention lowered rebleeding rate[31, 34, 36]. Meta-analysis by Yung *et al*[17] reported that specific treatment did not have significant effect on risk of rebleeding, while Tziatzios *et al*[19] reported that studies with positive CE who received specific treatment had significantly lower risk of rebleeding than no intervention. This suggests that if bleeding lesion is identified from CE and specific treatment is done, it could lower the risk of rebleeding.

We also added this in conclusion

Clinicians must consider various factors when stratifying OGIB patients who are at risk of rebleeding. Identifying the source of bleeding is essential as it provides treatment guide to which specific treatment intervention is needed. However, diagnostic yield of capsule endoscopy can vary and isolated small bowel lesions can be missed if it is not captured during the limited amount of time the capsule passes, presence of bubbles or debris can reduce visibility and targeted observation is impossible as movement of capsule depends solely on peristaltic movement of the intestine. Once the lesion is identified, targeted treatment can be applied and studies have shown that appropriate intervention can reduce the risk of rebleeding[31, 34, 36, 49]. Long term (more than 2 years) observational studies have shown that rebleeding can occur even in cases of negative CE, findings which suggests that negative CE does not imply absence of bleeding lesion. However, negative predict value of normal CE is high and studies have shown that rebleeding in patients with negative CE is lower compared to positive CE. Medications including steroids, NSAIDs, and anticoagulants are well known risk factors in overall GI bleeding and studies have shown that anticoagulants are also associated with risk of rebleeding in OGIB[26, 33, 34].

Many studies from eastern and western countries have analyzed different factors associated with rebleeding but limited number of meta-analysis data and discrepancies between studies provide challenge to creating generalized risk prediction. As such, the authors of different prediction models described in this article used the pool of data from their centers, grouped patients into rebleeding and non-rebleeding, analyzed risk factors from that patient population and created prediction model that best identify high risk patients. With the exception of ORBIT score that was created to assess generalized bleeding risk, other scores were targeted specifically for OGIB patients and Ohmiya index only uses comorbidities as variables in prediction model. Other prediction models include CE findings or specific treatment interventions as part of variables which means that patients must undergo CE and DAE must be available in order to identify patients at high risk of rebleeding. However, CE and DAE are not available in resource limited centers and primary

physicians, so ORBIT score or Ohmiya index may be used as an alternative measure. When available, RHEMITT score, PRSBB score, and prediction model using 5 variables may be more appropriate for OGIB patients but lack of external validation for PRSBB score and prediction model using 5 variables limits generalized use. This is why RHEMITT score looks promising as high AUROC has also been validated in two other validation studies.

Entire introduction was modified, references were reviewed and revised

Reviewer 2: We agree that the diagnosis and treatment of OGIB have markedly progressed. however, rebleeding sometimes occurs, and most rebleeding cases are difficult to diagnose and treat. Thus, it is important to identify the characteristics of cases in which rebleeding occurs. This article is well described for prediction models for recurrence in patients with small bowel bleeding OGIB is classified into two subtypes i) overt bleeding,; and ii) occult bleeding, Furethermore, overt bleeding is further divided into two groups: i) overt ongoing bleeding (continuous bleeding); and ii) overt previous bleeding (previous bleeding). Baba et al described patients with OGIB with overt previous bleeding had a higher risk of rebleeding.(Intern Med. 2020 Jun 1;59(11):1345-1350) Please discussed the rebleeding risk about type of OGIB..

Answer: Thank you for valuable comments. We agree with your comments, and there are different factors to consider that are well known risk factors of rebleeding. As you commented, type of presentation (overt or occult, further grouped into ongoing and previous overt by Baba et al.(Intern Med. 2020 Jun 1;59(11):1345-1350) is common risk factor for rebleeding which is why it is included in prediction models using 5 factors, and PRSBB score. Accordingly we have added a section about risk factors of bleeding immediately after introduction, which include CE findindgs, occult and overt bleeding, and therapeutic interventions.

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