

Name of Journal: World Journal of Gastrointestinal Endoscopy

Manuscript ID: 00038999

Title: Endoscopic management and outcome of non-variceal bleeding in patients with liver cirrhosis: a systematic review

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Dear editor,

We would like to thank the reviewers for a thorough review of our paper. Hereby we provide a point-to-point response to the points raised by the reviewers.

Reviewer #1:

We would like to thank the reviewer for the positive feedback and comments.

Reviewer #2:

1. Search scope, start and end time should be clearly marked.

Answer: Start date: 01/01/1980, End date: 01/01/2021. We have amended this in the manuscript during our revision.

2. It is suggested to combine the existing data on mortality and recurrence rates.

Answer: We would like to thank the reviewer for this comment. It would be interesting to combine those two parameters but there are several problems. Firstly some studies do not include mortality and/or recurrence rates, namely Paquet et al, Labenz et al, Schuman et al, Ikeda et al, Dulai et al, Sato et al 2005, Higuchi et al, Lecleire et al 2008, Smith et al, Fuccio et al, Awad et al and Gad et al. Secondly there

are studies (eg. Sato et al, Seo et al, Gonzalez et al, Rudler et al) which do not make clear how many patients of those who died experienced a rebleeding episode during the course of their disease [1-4]. Finally, Morsy et al do report that early rebleeding was a significant risk factor for in-hospital mortality as 30.8% of deaths occurred in patients who rebled. Moreover, Yang et al and Kuo et al state that rebleeding was a risk factor for in-hospital mortality in univariate and multivariate analysis respectively but do not report rates of rebleeding in those who died (only odds ratio). Last but not least Ardevol et al use the term “further bleeding” to define failure to control bleeding and early rebleeding (1-5 days) whereas rebleeding was defined as bleeding re-occurring between 5-45 days.. Further bleeding was reported as the cause of death in 10/24 patients who died but again it includes both failure and early rebleeding.

As such, we believe that existing data preclude the combination of mortality and recurrence rates and thus it is very difficult to recalculate rebleeding and death combined without access to the primary data of the studies.

3. Exclusion criteria in this manuscript only exclude pure variceal bleeding, other causes combined with variceal bleeding should also be excluded.

Answer: Indeed we only report exclusion of pure variceal bleeding. Although not stated in our elimination criteria, studies included in our review usually excluded patients with variceal bleeding (whether as the only source or as a possible combined source of bleeding) or grouped these patients in a deferent cohort (eg Seo et al, Schuman et al, Ardevol et al). In case of non-variceal bleeding most of the studies also report the presence or absence of varices during endoscopy and if varices were documented their had to be no variceal bleeding at the time of

endoscopy and no variceal bleeding stigmata. Ardevol et al, for example, report that 25 patients with upper GI bleeding had coexisting peptic ulcer and varices none of which with bleeding stigmata. Thus the episode of upper GI bleeding was attributed to peptic ulcer as per current guidelines which state that when no bleeding stigmata is observed, variceal haemorrhage can only be diagnosed in the absence of any other potential source of bleeding [5]. Finally studies that do not clearly report exclusion of variceal bleeding in their methods also do not report any active or possible bleeding from oesophageal varices in their endoscopic results (eg Sato et al 2005 and 2012, Fuccio et al, Higuchi et al, Lecleire et al 2009). In conclusion, cases included in our review seem to report sole non-variceal bleeding only and exclude cases with variceal bleeding as a combination.

Science editor:

1. Linguistic corrections have been done and unfinished sentence in start of page 3 amended.
2. A paragraph has been added in methods marking start and end time of study
3. A separate paragraph is now included in start of discussion describing mortality and rebleeding rates to help the reader.

Sincerely yours

October,08,2021

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