

Dear Editor,

This is a response letter accompanying the resubmission of our manuscript “The role of band ligation for secondary prophylaxis of variceal bleeding”. We are very happy to resubmit the revised manuscript and we would like to thank you and the Reviewers and the Editor for reading and making valuable comments on it. We provide point by point the answers to the reviewers’ comments. All changes are highlighted in the revised manuscript.

## **REVIEWER 1**

### **Major comments**

#### **Comment 1**

The present study reviews the role of band ligation in secondary prophylaxis of variceal bleeding. In my opinion the review does not add to the current knowledge and does not conclude anything different to what is already stated in guidelines (Baveno). Currently, the role of banding for 2ary prophylaxis is unquestionable as many papers/meta-analysis have already shown. So, a 2018 review going deep into differences between banding and a poupourri of alternative treatments that have already been demonstrated to be inferior, has no interest in my opinion. Band ligation is the best endoscopic strategy for variceal eradication, so the debate is not on banding but on additional therapies improving secondary prophylaxis. In this sense, a more interesting review would be based on the direction where secondary prophylaxis must

go besides band ligation.

### **Answer 1**

We agree that the role of band ligation is well established in the setting of secondary prevention of variceal bleeding in patients with liver cirrhosis nowadays. In our opinion there are some open issues as the postbanding bleeding (Aliment Pharmacol Ther. 2005 Jun 15;21(12):1435-43, Hepatology. 2006 Jan;43(1):196-7), the rising of the portal pressure following endoscopic procedures on the varices (Hepatology. 2004 Jun;39(6):1623-30) and most importantly the role of ligation on survival (Hepatology. 2008 Aug;48(2):580-7). For these reasons we believe that its role on secondary prevention needs further evaluation performing new RCTs and reviews/metanalyses adding new data if available. We have conducted this review adding data from 10 randomized studies and 11 metanalyses not included in previous manuscripts and we have carefully interpreted them to explore their contribution in the relevant literature adding our opinion for innovative endoscopic techniques. So, we believe that this manuscript is useful for the every-day clinical practice and can inspire for future research.

### **Comment 2**

Recent important studies which are not cited in this review, have shown the points to improve secondary prophylaxis:

- Early TIPS in patients at high-risk of re-bleeding

**Answer 2**

International guidelines state that early-TIPS placement must be considered in high-risk patients with cirrhosis, experiencing variceal bleeding. The results of the studies have examined the efficacy of early TIPS reported that it demonstrates control of acute variceal bleeding and a favorable effect on survival in high-risk patients with severe acute variceal bleeding. However, the effect of treatment in patients with acute variceal bleeding is beyond the scope of this review. Nevertheless, we have added an interesting recent meta-analysis which examined the efficacy of TIPS compared to endoscopic treatment (band ligation, endoscopic sclerotherapy and cyanoacrylate injection) for the secondary prevention of variceal bleeding, the incidence of post-treatment hepatic encephalopathy and the survival of cirrhotic patients. The results of this meta-analysis demonstrated a favorable effect of covered TIPS in patients with severe liver disease. This information was added in the discussion section (*page 16, line 28*).

**Comment 2**

- Addition of simvastatin to band ligation and  $\beta$ -blockers.

**Answer 2**

We thank the reviewer for this interesting point. We have added these data in the discussion section (*page 18, line 1*).

***Comment 3***

- HVPG-guided therapy to maximize HVPG decrease: important role of carvedilol.

**Answer 3**

We have added the role of HVPG-guided therapy and the importance of carvedilol in the reduction of HVPG in the discussion section (*page 18, line 10*).

**Minor comments*****Comment 1***

- Mortality of the bleeding episode is 12-16% in most recent studies instead of 20%. It largely depends on the cohort analyzed (proportion of advanced HCC).

**Answer 1**

We have changed as suggested (*page 13, line 2*).

***Comment 2***

-  $\beta$ -blockers instead of  $\beta$  blockers.

**Answer 2**

We have made the replacement throughout the manuscript as suggested.

**REVIEWER 2****Minor comments***Comment 1*

In literature search according, inclusion criteria just patients with liver cirrhosis could be included. But in papers 26 and 27 patients with schistosomiasis are included as well.

**Answer 1**

We thank the reviewer for bringing to our attention this inconsistency. The studies by El Amin et al, 2010 and Harras et al, 2010 included patients with schistosomiasis, therefore we excluded them from our analysis. One more study (Luz et al, 2011) included patients with schistosomiasis. However, in this study, there is a subgroup analysis excluding these patients. So, we have changed these data throughout the manuscript and the tables accordingly as suggested.

*Comment 2*

Carvedilol might be more potent in decreasing portal pressure when compared to conventional NSBB. This could be more discussed by authors. (Lo HG et al 2012: Randomized, controlled trial of carvedilol versus nadolol plus isosorbide mononitrate for the prevention of variceal rebleeding).

**Answer 2**

We have added the beneficial role of carvedilol in the reduction of portal pressure, as suggested in the discussion section (*page 18, line 10*). However, we have not cited the proposed study because of the lack of portal pressure measurement.

**Comment 3**

One more point could be discussed as simvastatin could decrease survival in patients with risk of rebleeding from esophageal varices (Abralde JG et al Gastroenterology 2016: Addition of Simvastatin to Standard Therapy for the Prevention of Variceal Rebleeding Does Not Reduce Rebleeding but Increases Survival in Patients with Cirrhosis.)

**Answer 3**

We have added these interesting data in the discussion section (*page 18, line 1*).

**REVIEWER 3****Minor comments****Comment 1**

A recent advance should be further discussed in the review.

The authors cited an important meta-analysis paper (Albillos A, Zamora J, Martinez J, Arroyo D, Ahmad I, De-laPena J, et al. Stratifying risk in the prevention of recurrent

variceal hemorrhage: results of an individual patient meta-analysis. HEPATOLOGY 2017;66:1219-1231). The authors correctly mentioned the words "in compensated patients the combination therapy was more effective in preventing rebleeding but had no influence in mortality rates [23]. In decompensated patients, band ligation alone demonstrated an increased risk of rebleeding and mortality compared to combination therapy [23]". In my opinion, this point deserves further discussion. Albillos et al. found that additional use of EVL might have a higher mortality (incidence rate ratio, 1.40; 95% confidence interval [95% CI], 0.87-2.27) and risk of all-source rebleeding (incidence rate ratio, 1.36; 95% CI, 0.87-2.14) and variceal rebleeding (incidence rate ratio, 1.24; 95% CI, 0.75-2.05) in patients with Child-Pugh class B/C who received NSBBs; but the difference was not statistically significant.

#### **Answer 1**

We have discussed this interesting finding by Albillos et al, in greater detail in the discussion section (*page 14, line 10*).

#### **Comment 2**

Additionally, in a randomized controlled trial (Villanueva C, Graupera I, Aracil C, Alvarado E, Minana J, Puente A, et al. A randomized trial to assess whether portal pressure guided therapy to prevent variceal rebleeding improves survival in cirrhosis. HEPATOLOGY 2017;65:1693-1707.), which was not cited in the present review, Villanueva et al. found that the hemodynamic response-guided therapy group had a significantly lower risk of rebleeding (hazard ratio, 0.53; 95% CI, 0.29-0.98), further decompensation (hazard ratio, 0.68; 95% CI, 0.46-0.99), and mortality (hazard ratio,

0.59; 95% CI, 0.35-0.99) than the conventional treatment group. Notably, in the hemodynamic response–guided therapy group, hemodynamic responders and nonresponders received NSBB alone and in combination with EVL, respectively; by comparison, in the conventional treatment group, all patients received a combination of NSBB and EVL. Thus, it might be reasonable to conclude that additional EVL would not be beneficial for improving the outcomes if there was no hemodynamic response to NSBB. These considerations had been discussed in a recent correspondence (Qi X, Méndez-Sánchez N, Mancuso A, Romeiro FG, Guo X. Who should receive endoscopic variceal ligation after recovering from acute variceal bleeding? *Hepatology*. 2018 May;67(5):2057-2058.). They should be further added. These considerations suggested the insufficient role of EVL in secondary prevention of variceal bleeding. They should be discussed.

## **Answer 2**

We have added and discussed these considerations in the discussion section (*page 18, line 20*).

## **EDITOR COMMENTS**

We have revised our manuscript according to Systematic Review format as suggested.

We look forward to hearing from you regarding our revised manuscript. We would be glad to respond to any further questions and comments that you may have.

Yours sincerely

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