Ruo-Yu Ma
Science Editor
World Journal od Gastrointestinal Endoscopy.

Dear Editor,

Thank you for the helpful comments from the two reviewers of our paper. We have replied in detail to each of the comments from the reviewers and our responses are pasted below. We have added a multivariate analysis of the data as requested by **reviewer #1** and although the results are not significant, we have included the new table in the revised manuscript (Table 4)

Further changes as suggested by the reviewers are highlighted in yellow in the revised manuscript which is attached

Page 2 Materials and Methods: A prospectively documented single-center database was used to retrospectively identify all patients with BEV who were treated with EVL between 2000 and 2018.

Page 5 All patients were given non-selective β–blockers (NSBB) during follow-up unless specifically contra-indicated.

Page 5 Data analysis The Student t-test and χ^2 test were used when appropriate and the Kaplan–Meier method was used to estimate the cumulative incidence of re-bleeding and actuarial survival. Multivariate analysis was used to assess risk factors for rebleeding

Page 8 No significant specific risk factors for rebleeding were evident on multivariate analysis (Table 4)

Reviewer #1:
Dear authors It is an interesting and well organized study about the role and the significance of band ligation on the management of variceal bleeding, as well as on variceal eradication. I agree that the use from your team of a standard and well defined protocol for the management of variceal bleeding is of great importance. However, I have some comments to make:

Reviewer #1 You mention that all of your patients had taken B-blockers.
Authors Response: The manuscript states that all patients were given B-blockers **unless there were specific contra-indications.** Fourteen patients were not given B-blockers because of specific contra-indications which included asthma, sinus bradycardia, symptomatic peripheral vascular diseases, advanced heart failure, atrioventricular block, spontaneous bacterial peritonitis and refractory ascites. Subsequently a further 12 patients were intolerant to either propranolol or carvidelol and stopped their medication due to shortness of breath, intractable portosystemic encephalopathy, lethargy, tiredness, insomnia or impotence.
Reviewer #1 Which was the mean dose?
Authors Response: Propranolol and carvedilol were both used in this patient cohort. Propranolol was started at 10 mg given three times a day orally, then adjusted according to the BP and HR to a mean dosage of 40 mg twice daily.

Carvedilol was started at 6.25 mg a day orally, then advanced to 12.5 mg/day thereafter orally adjusted according to the BP, HR.
How many of them had been well controlled (cardiac rate < 55-60 /min) and how many had been not? Had this any effect on the rates of controlling bleeding, on the rates of rebleeding and mortality?
Authors Response: About 80% were well controlled with a heart rate of 55-60 / min and 20% not. This had no significant effect on the rates of controlling bleeding, rebleeding and mortality
Reviewer #1 What kind of b-blocker had you prescribed? Propranolol or carvedilol? Was there any difference between those receiving propranolol and those receiving carvedilol?
Authors Response: Propranolol and carvedilol were both used in this patient cohort (see above). There was no significant difference due to the small numbers in the final groups
Reviewer #1 Which were the independent factors associated with increased rebleeding rates and mortality? You had separated patients according to Child-Pugh stage and you outlined the mortality rates of each group. But this is not enough. Age, sex, MELD score, C-P grade, etiology of liver disease, favourable response to b-blockers, had any effect on rebleeding rates and mortality? A multivariate analysis is needed.
Authors Response: A multivariate analysis was done as advised and is included in the revised manuscript.

Reviewer #2:
This study aimed to investigate the efficacy of endoscopic variceal ligation (EVL) in controlling acute variceal bleeding, preventing variceal recurrence and rebleeding and achieving complete eradication of esophageal varices in patients who present with bleeding esophageal varices. The authors analyzed a database which was recorded for 19 years and study included 140 patients. They showed a significant effort to analyze and present this data. However, there are some major problems in their methods, presentation and writing the manuscript.
Reviewer #2 1.This is clearly a retrospective analysis of a database, however, the authors define it as a prospective study.
Authors Response: Thank you for this comment. The text has been amended to reflect “a retrospective analysis of a prospectively documented and recorded database”
Reviewer #2 2. The authors base their study that “….no studies have specifically evaluated detailed outcome in relation to the technical constraints imposed by the design of the ligating device which influences the effectiveness of EVL in controlling acute variceal bleeding…”. However, the study design and the data they presented is completely irrelevant with this main underlying objective.
Authors Response: We believe the study design and the data presented is completely relevant to the underlying objective as the intrinsic technical constraints imposed by the design of the ligating device has a direct bearing on outcome and thus influences the effectiveness of EVL in controlling acute variceal bleeding and in the technical ability to completely eradicate varices. In addition our data is strongly supported by the 17 randomised trials presented in Table 4 which show the significant inferiority in variceal eradication and recurrence when compared to sclerotherapy.

Reviewer #2 3. The effectivity of EVL was studied and published in many well-designed clinical studies, and this manuscript add nothing to current knowledge and clinical applications.

Authors Response: The large cohort presented and analysed in detail. The concluding paragraph highlights a new interpretation of these data. We emphasize that consistent with previous reports EVL in this study was safe with low procedure-related complication rates. While complete visual eradication of varices is more frequently achievable with IST and has consistently been used as the desired endpoint for endoscopic variceal intervention, this goal is not always attainable in EVL. As alluded to above, the inherent attributes of EVL and IST are dissimilar and complete eradication may not be achievable in all patients undergoing EVL. Overall four-fifths of patients in this study had EV that were easily managed and responded to β-blockers and EVL with no further bleeding after the initial index intervention. The remaining one-fifth however were complicated and had bleeding that was difficult to control in the short and long-term despite being on combination therapy. We have identified a subgroup of patients with small (Gr 1 and 2) varices where size and mucosal scarring preclude further safe banding. Importantly we have shown that these patients have “stable varices” with no rebleeding or progression which resulted in “functional eradication” despite the presence of residual small visible varices. The results of this study should stimulate further research to optimize robust and objective endpoints for reporting of EVL which are likely to differ from the historical outcomes reported in previous RCTs.

Reviewer #2 4. The title, the abstract and the whole manuscript is needed to review by a specialist in medical writing.

Authors Response: The whole manuscript, including title, abstract, methodology, statistics, results and discussion has been reviewed in detail by a senior English journal editor and found to be entirely satisfactory.

The revised manuscript is attached as well as a covering letter from the authors. Full additional documentation was submitted on 28-04-2020 with the original manuscript.

Yours sincerely
Professor Jake Krige