

Endoscopic ultrasound predicts early recurrence of esophageal varices after endoscopic band ligation: a prospective cohort study

Ankstyvas stemplės venų varikozės atsinaujinimas po endoskopinio perrišimo yra susijęs su specifiniais endoskopiniu ultragarsiniu tyrimu diagnozuojamais pakitimais: prospektyvusis tyrimas

Laura Mašalaitė^{1, 2}, Jonas Valantinas^{1, 2}, Juozas Stanaitis¹

¹ *Centre of Hepatology, Gastroenterology and Dietetics, Vilnius University Hospital "Santariskiu Klinikos", Santariskiu Str. 2, LT-08661 Vilnius, Lithuania*

² *Clinic of Gastroenterology, Nephrourology and Surgery, Medical Faculty, Vilnius University, Vilnius, Lithuania*
E-mail: lauramasalaite@yahoo.com

Background

Variceal recurrence following endoscopic treatment is very common and associated with the variceal bleeding or rebleeding risk. Esophageal collateral veins are observed by endoscopic ultrasound (EUS) in patients with portal hypertension. The aim of the study was to identify whether EUS findings could predict the early variceal recurrence after endoscopic band ligation (EBL).

Patients and methods

The prospective cohort study was performed, including consecutive patients, undergoing EBL for esophageal varices. EUS was performed before ligation, and the type and grade of esophageal collateral veins (ECV) were described. After all EBL sessions had been completed, patients were examined every three months for a 12-month period to detect variceal recurrence. Patients in whom varices reoccurred within six months were noted as the early recurrence group. The relationship between the type and grade of ECV and the early variceal recurrence was analysed to detect the possible risk factors. The study was approved by the local ethics committee.

Results

Forty patients were included in the study over the study period. Twelve of the forty patients (30%) had early variceal recurrence within six months, and nineteen of the forty patients (47.5%) had variceal recurrence within twelve months after EBL. Overall, the mean number of months from the end of EBL until recurrence was 7.26 ± 3.05 (3–12)). Severe peri-ECV were statistically significantly associated with the higher variceal recurrence risk within six months ($p = 0.041$), whereas severe para-ECV had no statistically significant risk related to the early variceal recurrence risk ($p = 0.149$).

Conclusions

A positive association between early variceal recurrence following endoscopic band ligation and specific findings on EUS was demonstrated. Severe-grade peri-ECV predict early variceal recurrence following EBL.

Key words: endoscopic ultrasound, variceal recurrence, endoscopic band ligation

Įvadas / tikslas

Pagrindinis stemplės venų varikozės gydymo metodas yra endoskopinis jų perrišimas guminiiais žiedais (toliau – endoskopinis perrišimas). Stemplės venų varikozės atsinaujinimas po endoskopinio gydymo yra dažnas ir jam būdingas didelis kraujavimo pavojus. Sergant kepenų ciroze su portine hipertenzija, aplink stemplę išsiplėčia kolateralinės venos, kurias galima matyti ir įvertinti atliekant endoskopinį ultragarsinį tyrimą. Šio darbo tikslas – nustatyti, ar endoskopinio ultragarsinio tyrimo metu matomas kolateralinių venų tipas ir dydis gali padėti prognozuoti ankstyvą stemplės venų varikozės atsinaujinimą po endoskopinio perrišimo.

Ligoniai ir metodai

Į prospektyvųjį tyrimą įtraukti ligoniai, kuriems buvo atliktas stemplės varikozinių venų endoskopinis perrišimas. Prieš perrišimą visiems pacientams buvo atliktas endoskopinis ultragarsinis tyrimas ir įvertintas aplink stemplę esančių venų tipas ir dydis. Po endoskopinio stemplės varikozinių venų perrišimo ligoniai buvo stebimi vienerius metus siekiant nustatyti stemplės venų varikozės atsinaujinimą. Atsinaujinimas, kuris išsivystė per 6 mėnesius po gydymo, buvo vadinamas ankstyvu. Siekiant nustatyti ankstyvo stemplės venų varikozės atsinaujimo rizikos veiksnius, buvo įvertintas kolateralinių venų ryšys su atsinaujinimu. Tyrimui atlikti buvo gautas regioninio biomedicininų tyrimų etikos komiteto leidimas.

Rezultatai

Po endoskopinio perrišimo 30 % pacientų (12 iš 40) išsivystė ankstyvas stemplės venų varikozės atsinaujimas. Didelės artimosios (*peri*) kolateralinės venos, diagnozuojamos atliekant endoskopinį ultragarsinį tyrimą, buvo statistiškai reikšmingai susijusios su didesne ankstyvo stemplės venų varikozės atsinaujimo rizika ($p=0,041$). Didelės tolimosios (*para*) kolateralinės venos, diagnozuojamos atliekant endoskopinį ultragarsinį tyrimą, nebuvo statistiškai reikšmingai susijusios su didesne ankstyvo atsinaujimo rizika ($p=0,149$).

Išvados

Šiuo tyrimu nustatyta, kad didelės artimosios kolateralinės venos yra susijusios su ankstyvu stemplės venų varikozės atsinaujimu po endoskopinio perrišimo.

Reikšminiai žodžiai: endoskopinis ultragarsinis tyrimas, stemplės venų varikozės atsinaujimas, endoskopinis perrišimas

Introduction

Gastroesophageal varices are the most relevant portosystemic collaterals in portal hypertension. Variceal bleeding is the most severe complication of cirrhosis and is related with a high mortality rate among these patients. The mortality rate in each episode is up to 30% [1] and 15–20% at six weeks [2, 3]. Recurrent bleeding is common without prophylactic treatment [4], indicating that the treatment of esophageal varices should be aimed at preventing variceal recurrence and rebleeding. Many kinds of collaterals develop in patients with portal hypertension for the reduction of a high portal pressure [5, 6, 7]. The detailed mechanism of variceal recurrence after endoscopic treatment is still not fully identified, but it seems to be related with these collateral veins.

Endoscopic band ligation (EBL) became the preferred method of treatment for esophageal varices, because it was proved in several randomized trials to be as effective as injection sclerotherapy with fewer serious adverse events, requiring fewer sessions to achieve eradication, but related to a higher frequency of recurrent

varices as compared with sclerotherapy [8, 9]. However, the recurrence of esophageal varices occurs, and the recurrence is associated with the variceal rebleeding risk. The reported rates of variceal recurrence after EBL range between 8–48% [10–12]. Since variceal recurrence following endoscopic treatment is inevitable, the determination of risk factors contributing to it may be of clinical significance.

The systematic analysis [13] of 13 studies analyzing gastroesophageal collateral veins as risk factors for variceal recurrence after endoscopic treatment showed that perforating veins and periesophageal collateral veins were related to a higher risk of variceal recurrence (OR = 3.93; 95 % CI 1.06–14.51; I² = 96 %; OR = 2.29; 95 % CI 1.58–3.33; I² = 55 %). These findings should be interpreted with caution because of the heterogeneity of the studies with regard to the method of treating varices, the time index when EUS was performed, the recorded EUS parameters, definitions of collateral veins, and the follow-up length. Only a few prospective studies with a small sample size evaluating the EUS risk factors for

variceal recurrence following endoscopic band ligation have been published [14–17].

The aim of the present study was to evaluate whether the type and grade of esophageal collateral veins detected by EUS can predict the early recurrence of esophageal varices in patients treated by EBL.

Patients and methods

Inclusion / exclusion criteria

Patients with esophageal varices treated by EBL from September 2011 to June 2013 were prospectively enrolled in this cohort study. The inclusion criteria were as follows: (1) aged over 18 years; (2) liver cirrhosis with intrahepatic portal hypertension; (3) size of varices F2 or F3 according to the recommendations of the Japanese society for portal hypertension [18]; (4) primary or secondary variceal prophylaxis according to the Baveno V consensus [19]; (5) signed informed consent. The exclusion criteria were as follows: (1) age younger than 18 years; (2) refusal to participate in the study; (3) hepatocellular carcinoma stage C according to the Barcelona Clinic Liver Cancer classification [20]; (4) type 1 hepatorenal syndrome; (5) grade 3–4 of hepatic encephalopathy; (6) pregnancy; (7) severe comorbidities. The study was approved by the local ethics committee.

Pre-treatment evaluation included a detailed medical history, physical examination and the patients' age, gender, aetiology of liver cirrhosis and episodes of previous variceal bleeding. The use of non-selective beta-blockers was noted. Child–Pugh's score and the MELD (*Model of end-stage liver disease*) score were also estimated. A complete blood count, liver function tests, kidney function tests and abdominal ultrasound were carried out. Conventional endoscopy and endoscopic ultrasound had been performed before endoscopic band ligation. Patients received local oropharyngeal anaesthesia and intravenous sedation before endoscopic examinations.

Conventional endoscopy

Upper gastrointestinal endoscopy was performed to examine the esophagus for submucosal varices. The endoscopy had been performed before EUS and EBL in all patients with Olympus *Evis Exera* II videoendoscopes GIF–Q165 or GIF–H180. Esophageal varices

were evaluated according to the recommendations of the Japanese society for portal hypertension: localization, colour, size (F1, F2, F3), and the presence of red colour signs (RCS). The size of the varices was determined during withdrawal of the endoscope; also, as much air as possible was aspirated from the stomach while the esophageal lumen was fully inflated.

Endoscopic ultrasound (EUS)

Before EBL, all patients had undergone an EUS examination using a radial echoendoscope with the frequency of 12 MHz (Olympus GF–UE 160–AL5). EUS was performed by an independent endoscopist who was blinded to the patients' clinical data as well as to the results of conventional endoscopy. During the EUS examination, the presence of extra-luminal esophageal collateral veins was determined. Collaterals around the esophagus were scanned from the esophago-gastric junction, withdrawing the echoendoscope to the 5th proximal centimetre. Based on EUS findings, esophageal collateral veins (ECV) were classified into two types: peri-ECV and para-ECV (Fig. 1). The corresponding EUS images depicting peri-ECV and para-ECV are presented in Fig. 2. Peri-ECV were described as a group of small vessels adjacent to the *muscularis propria* layer. Para-ECV were described as a group of larger vessels away from the *muscularis propria* layer. Peri-ECV were classified as none,

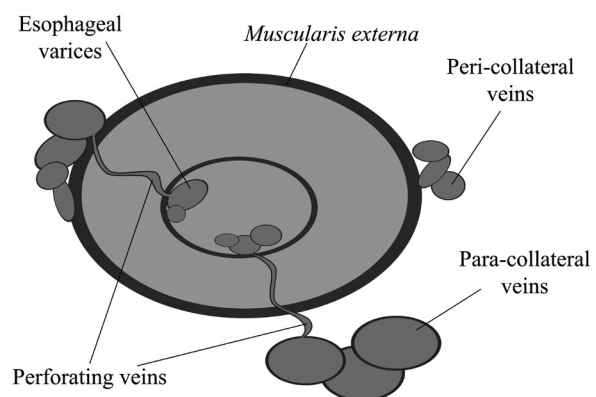


Fig. 1. Esophageal collateral veins detected by EUS: schematic picture

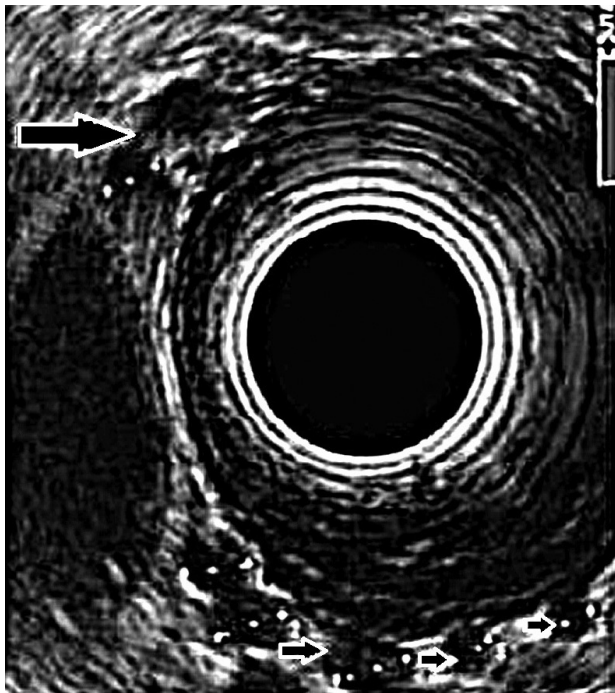


Fig. 2. EUS images: peri-ECV (short arrows) and para-ECV (long arrow)

mild (<2 mm) or severe (≥ 2 mm), and para-ECV were also classified as none, mild (<5 mm) or severe (≥ 5 mm).

Endoscopic band ligation and observation

The standard ligation technique was followed and multi-band EBL device was used (Super7, Boston Scientific). EBL was repeated at 2-week intervals until esophageal varices were eradicated. The eradication of varices was defined as non-visualization of varices in the distal esophagus or as varices too small for ligation.

After all EBL sessions had been completed, patients were observed for variceal recurrence and upper gastrointestinal endoscopy every three months until 12 months after the procedure had been performed. Recurrence of esophageal varices was defined as either the formation of new varices or the appearance of RCS. Patients in whom varices reoccurred within six months were ascribed to the early recurrence group. The relationship between the EUS findings prior to EBL and the esophageal varices recurrence rate and time was analysed. The flow diagram of the study is depicted in Fig. 3.

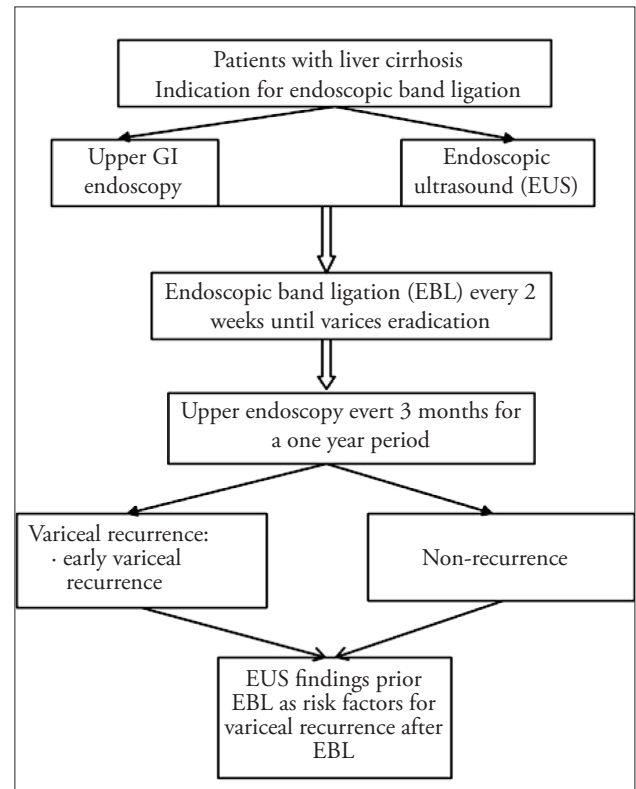


Fig. 3. The flow diagram of the study

Statistical analysis

Continuous variables are presented as mean and standard deviations. Student's t-test or the Mann–Whitney U test were used to compare the mean differences among the groups. Categorical variables were analysed by the Chi-square or Fisher's exact tests. The recurrence-free survival curve was generated using the Kaplan–Meier method. The statistical analyses were performed with an SPSS program (v17). A p value of less than 0.05 was considered statistically significant.

Results

During the study period, forty patients (28 men (70%) and 12 women (30%) with the average age of 54.1 ± 9 years, range 35–77 years, were enrolled in this prospective study. The cause of portal hypertension in all patients was alcohol-related liver cirrhosis (47.5%, $n = 19$), namely hepatitis C cirrhosis (37.5%, $n = 15$), primary biliary cirrhosis (5%, $n = 2$) and cryptogenic liver cirrhosis (10%,

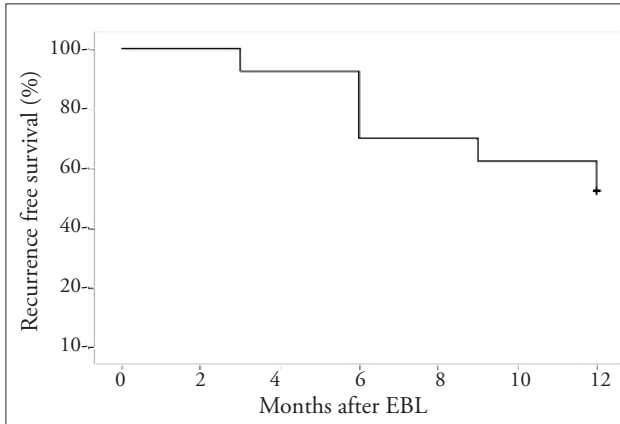


Fig. 4. Variceal recurrence-free survival; EBL – endoscopic band ligation

$n = 4$). The main indication for EBL was secondary prophylaxis (57.5%, $n = 23$), followed by primary prophylaxis (42.5%, $n = 17$). The size of the varices before treatment was F2 in 24 patients (60%) and F3 in 16 patients (40%), and 77.5% of them had RCS. Overall, we performed 89 EBL procedures and placed 422 rubber bands. The mean number of bands placed during the one EBL session was five (range, 2–9), and the mean number of EBL sessions to achieve variceal obliteration was 2.13 ± 0.82 (range, 1–5). All patients achieved variceal eradication and were regularly checked for recurrence following EBL throughout the one-year period.

During the follow-up period, 19 patients had variceal recurrence (47.5%). The mean number of months from the end of EBL until variceal recurrence was 7.26 ± 3.05

(range, 3–12). Recurrence of esophageal varices was detected in 3 (7.5%) of the 40 patients within three months, in 12 (30%) within six months, in 15 (37.5%) within nine months, and in 19 (47.5%) of the 40 patients within one year of EBL. 21 patients were recurrence-free after one year. The recurrence-free survival curve was generated by the Kaplan–Meier method and is presented in Fig. 4.

Regarding the recurrence of esophageal varices, the patients were divided into the early variceal recurrence group ($n = 12$) and the group of recurrence within 12 months ($n = 19$). The early variceal recurrence was defined as recurrence within six months or less.

Comparison of EUS findings

The EUS findings obtained prior to EBL were compared between the early variceal recurrence group and all patients who had variceal recurrence within 12 months. Severe peri-ECV cases were statistically significantly associated with a higher variceal recurrence risk both within six months ($p = 0.041$) and within 12 months ($p < 0.001$). Severe para-ECV cases were statistically significantly associated with the higher variceal recurrence risk only within 12 months ($p = 0.018$) and had no statistically significant risk related to the early variceal recurrence risk within six months ($p = 0.149$) (Table 1).

Discussion

Since variceal recurrence following endoscopic treatment is inevitable, the determination of risk factors contributing to it is of clinical significance.

Table 1. Outcome at 6 and 12 months in patients with non/mild or severe ECV

	Non/mild peri-ECV $n = 20$	Severe peri-ECV $n = 20$	p value	Odds ratio (95% CI)
Recurrence (%):				4.64
· within 6 months	3 (15)	9 (45)	0.041	(1.02–21.00)
· within 12 months	3 (15)	16 (80)	<0.001	22.67 (4.37–117.47)
	Non/mild para-ECV $n = 35$	Severe para-ECV $n = 5$	p value	Odds ratio (95% CI)
Recurrence (%):				4.33
· within 6 months	9 (25.7)	3 (60)	0.149	(0.62–30.25)
· within 12 months	14 (40)	5 (100)	0.018	16.31 (0.84–318.14)*

* Before calculations, the frequency of 0.5 had been added to all frequencies in 2×2 tables whenever a cell was empty.

The available evidence suggests that the type and grade of collateral veins on EUS predisposes to the recurrence of esophageal varices after endoscopic treatment. Several investigators have pointed out a relationship between extra-esophageal collateral veins and the recurrence of esophageal varices after endoscopic treatment. It is very difficult to analyse and combine the results of these studies because of their heterogeneity, especially regarding the follow-up length and the treatment method of varices. The majority of the studies have analysed variceal recurrence and the related EUS risk factors following sclerotherapy or a combined endoscopic treatment. Only a few of them have analysed variceal recurrence and the related EUS risk factors following EBL [14–17]. The treatment method is important because the effects of sclerotherapy and EBL on esophageal varices are different, which is why studies showed different results for the prevalence and predictive value of collateral veins.

Our study has demonstrated that the early variceal recurrence after EBL is associated with the presence of a severe-grade peri-ECV on EUS before EBL. The results of our study coincide with the results of other authors who have investigated pre-treatment EUS findings in relation with variceal recurrence after EBL. It is difficult to compare our results with the results of similar studies because of differences regarding the follow-up length and the definitions of collateral veins.

To our knowledge, the last published study about the EUS role in predicting variceal recurrence following EBL was carried out by Kume et al. in 2012 [14]. They have reported that severe esophageal collateral veins and perforating veins by EUS before EBL predict a long-term endoscopic recurrence of esophageal varices. Konishi et al. [15] performed the first study to show the importance of pre-treatment EUS in assessing the relationship between the cardiac vascular structures and the recurrence of esophageal varices after EBL. This short-term follow-up study has revealed that the presence of severe grade cardiac perforating veins is strongly associated with an early (within three months) recurrence of esophageal varices following EBL, other than those with mild perforating veins (90.9% vs 21%, $p < 0.01$). Leung et al. and Lo et al. [16, 17] reported that the rates of recurrent varices and recurrent bleeding were significantly higher in patients with the severe-

grade para-ECV. In the latter studies, the para-ECV corresponded to the peri-ECV in our study.

Our study had several limitations. A larger sample size and a longer follow-up period would be more appropriate, but in our case we had some limitations regarding the study duration. Another limitation was that we had no possibility to use a mini-probe echoendoscope with a higher frequency for a more accurate evaluation of esophageal collateral veins. The evaluation for variceal recurrence after EBL is relatively subjective and poses some difficulties to the decision whether or not esophageal veins have reoccurred. Also, in different studies the definitions of variceal recurrence are different. We believe that more objective parameters would be more appropriate; for example, the recurrence of varices may be defined as varices which could be ligated. On the other hand, this study was the first in Lithuania in which we used the EUS as the diagnostic tool for portal hypertension.

The current study presents the information that may be important for selecting the optimal treatment for esophageal varices. The esophageal varices that show mild collateral veins on EUS before EBL may be appropriate for EBL. On the other hand, esophageal varices with other types of ECV on EUS may be suitable for a combined endoscopic treatment. EUS could be used to better evaluate the risk of recurrence and rebleeding of esophageal varices. It could also help to identify patients who are at risk of variceal recurrence and rebleeding and to choose the proper endoscopic and/or medical treatment and surveillance according to the risk of variceal recurrence. Furthermore, it could be used to approve the surveillance protocols and to determine indications for EBL or endoscopic sclerotherapy, to reduce mortality and, finally, to prolong the waiting time for liver transplantation.

The role of EUS in predicting variceal recurrence after endoscopic treatment in patients with portal hypertension remains to be investigated in future studies, especially the role of EUS in improving the survival rate of patients with esophageal varices. Specific situations in which we could strongly recommend using ES have not yet been clearly defined. New indications can be developed in future after an adequate experimental validation.

Conclusions

A positive association between early variceal recurrence after EBL and the type and grade of collateral veins investigated by EUS has been demonstrated. Severe peri-ECV have been found to be statistically significantly associated with the early variceal recurrence risk after EBL. EUS is a promising tool for predicting the recurrence of esophageal varices following the endoscopic treatment. The further research should address the relation between

EUS and the recurrence of esophageal varices in other types of treatment and establish surveillance protocols for the recurrence.

Acknowledgements

Laura Mašalaitė, Jonas Valantinas, Juozas Stanaitis declare that they have no ethical conflicts and have no conflicts of interests. No funding of this work has been received .

REFERENCES

- Graham DY, Smith JL. The course of patients after variceal hemorrhage. *Gastroenterology* 1981; 80(4): 800–809.
- D'Amico G, De Franchis R. Upper digestive bleeding in cirrhosis. Post-therapeutic outcome and prognostic indicators. *Hepatology* 2003; 38: 599–612.
- Stokkeland K, Brandt L, Ekblom A, Hultcrantz R. Improved prognosis for patients hospitalized with esophageal varices in Sweden 1969–2002. *Hepatology* 2006; 43(3): 500–505.
- Augustin S, González A, Genescà J. Acute esophageal variceal bleeding: Current strategies and new perspectives. *World J Hepatology* 2010; 2(7): 261–274.
- Caletti GC, Brocchi E, Ferrari A, Fiorino S, Barbara L. Value of endoscopic ultrasonography in the management of portal hypertension. *Endoscopy* 1992; 24: 342–346.
- Irisawa A, Obara K, Sato Y et al. An endoscopic analysis of collateral veins inside and outside the esophageal wall in portal hypertension. *Gastrointest. Endosc.* 1999; 50: 374–380.
- Kassem MA, Salama AZ, Rosch T. Endoscopic ultrasonography in portal hypertension. *Endoscopy* 1997; 29: 399–406.
- Sarin SK, Govil A, Jain AK, et al. Prospective randomized trial of Endoscopic sclerotherapy versus variceal band ligation for esophageal varices: influence on gastropathy, gastric varices and variceal recurrence. *J Hepatol* 1997; 26: 826–832.
- Hou MC, Lin HC, Lee FY, Chang FY, Lee SD. Recurrence of esophageal varices following endoscopic treatment and its impact on rebleeding: comparison of sclerotherapy and ligation. *J Hepatol* 2000; 32: 202–208.
- Stiegmann GV, Goff JS, Michaletz-Onody PA, Korula J, Lieberman D, Saeed ZA, Reveille RM, Sun JH, Lowenstein SR. Endoscopic sclerotherapy as compared with endoscopic ligation for bleeding esophageal varices. *N Engl J Med* 1992; 326 (23): 1527–1532.
- Hou MC, Lin HC, Kuo BI, Chen CH, Lee FY, Lee SD. Comparison of endoscopic variceal injection sclerotherapy and ligation for the treatment of esophageal variceal hemorrhage: a prospective randomized trial. *Hepatology* 1995; 21(6): 1517–1522.
- Lahbabi M, Mellouki I, Aqodad N, Elabkari M, Elyousfi M, Ibrahim SA, Benajah DA. Esophageal variceal ligation in the secondary prevention of variceal bleeding: Result of long term follow-up; *Pan African Medical Journal* 2013; 15: 3.
- Masalaite L, Valantinas J, Stanaitis J. The role of collateral veins detected by endosonography in predicting the recurrence of esophageal varices after endoscopic treatment: a systematic review. *Hepatol Int* 2014; 8 (3): 339–351.
- Kume K, Yamasaki M, Watanabe T, Yoshikawa Y, Otsubuki M and Harada M. Mild collateral varices and a fundic plexus without perforating veins on EUS predict endoscopic non-recurrence of esophageal varices after EVL. *Hepato-Gastroenterology* 2011; 58: 798–801.
- Konishi Y, Nakamura T, Kida H, Seno H, Okazaki K, Chiba T. Catheter US probe EUS evaluation of gastric cardia and perigastric vascular structures to predict esophageal variceal recurrence. *Gastrointest Endosc* 2002; 55: 197–203.
- Leung V, Sung J, Ahuja AT, et al. Large paraesophageal varices on endosonography predict recurrence of esophageal varices and rebleeding. *Gastroenterolog*, 1997; 112: 1811–1816.
- Lo GH, Lai KH, Cheng JS, Huang, Wang SJ, Chiang HT. Prevalence of paraesophageal varices and gastric varices in patients achieving variceal obliteration by banding ligation and by injection sclerotherapy. *Gastrointest Endosc* 1999; 49: 428–436.
- Tajiri T, Yoshida H, Obara K, et al. General rules for recording endoscopic findings of esophagogastric varices (2nd edition). *Digest Endosc* 2010; 22: 1–9.
- de Franchis R. Revising consensus in portal hypertension: Report of the Baveno V consensus workshop on methodology of diagnosis and therapy in portal hypertension. *Journal of Hepatology* 2010; 53: 762–768.
- Forner A, Reig ME, de Lope CR, Bruix J. Current strategy for staging and treatment: the BCLC update and future prospects. *Semin Liver Dis* 2010; 30: 61–74.