ISSN: 2091-2331 (Print) 2091-234X (Online)

Journal of Nobel Medical College

Volume 08, Number 02, Issue 15, July-December 2019, 15-20

Original Article

Non-Invasive Predictors of Esophageal Varices in Alcoholic Chronic Liver Disease

Rishab Shrestha*[1], Alisha Rajbhandari[2], Pradip Chaudhary[1]and Kausal Sigdel[1]

[1]Department of Internal Medicine, [2]Department of Nursing, Nobel Medical College Teaching Hospital, Biratnagar, Nepal.

Article Received: 15th October, 2019; Accepted: 12th December, 2019; Published: 31st December, 2019

DOI: http://dx.doi.org/10.3126/jonmc.v8i2.26717

Abstract

Background

Alcohol is widely consumed socially accepted recreational beverage, that is toxic and affects directly or indirectly almost every organ. Spectrum of alcoholic liver disease ranges from fatty liver to cirrhosis. One of the complications of the later spectrum is portal hypertension, around 50% develops varices and bleeding depends on the size of the varices. Predicting varices without endoscopic is difficult but few non-invasive parameters are available.

Materials and Methods

It was a prospective cross-sectional study done in Nobel Medical College Teaching Hospital, Biratnagar, Nepal from September 2018 to August 2019. Approval was acquired from Institutional Review Committee. Patients with chronic ethanol ingestion and features suggestive of chronic liver disease clinically and investigation wise were enrolled in the study. History, physical examinations along with platelet count, prothrombin time was taken and ultrasonography abdomen and upper gastrointestinal endoscopy was done to see the splenic diameter, and varices.

Results

Esophageal varices were present in 53%. Mean platelet count with varices was 122566 ± 36024.8 /mm^3, splenic diameter was 133.1 ± 21.3 mm, prothrombintime (PT) time was 19.3 ± 5.0 sec and ratio of platelet per spleen diameter was 930.2 ± 259.4 /mm^3/mm. Platelet count < 163500/mm^3 has sensitivity and specificity 83.0% and 83.0% respectively. Ratio of platelet per splenic diameter ratio cutoff 1293.7 has 88.7% sensitivity and 85.1% specificity for predicting varices.

Conclusion

In chronic alcoholic liver disease patients low platelet count, increased splenicdiameter, low platelet per splenic diameter ratio are useful in predicting presence of esophageal varices.

Key words: *Cirrhosis, Platelet count, Portal hypertension, Varices*

***Corresponding author**
Dr. Rishab Shrestha
Lecturer
Email: risj_shr@hotmail.com
ORCID: https://orcid.org/0000-0003-0684-4186

Citation
Shrestha R, Rajbhandari A, Chaudhary P, Sigdel K, Non-Invasive Predictors of Esophageal Varices in Alcoholic Chronic Liver Disease, JoNMC. 8:2 (2019) 15-20.

Introduction

Alcohol is widely consumed recreational beverage that is toxic to humans. It's a socially accepted widely consumed drug that affects directly or indirectly almost every organ of the human body. Here Alcohol refers to primary alcohol Ethanol (ethyl alcohol). Liver plays a vital role in metabolism of alcohol, except 10% of ingested alcohol eliminated through lungs, kidneys and skin, all remainder has to get oxidized through three different pathways that occur in liver. Chronic alcohol ingestion causes accumulation of toxic metabolites in liver causing liver injury. Alcohol related liver disease encompasses a spectrum of injury, ranging from simple steatosis to frank cirrhosis, depending on various risk factors other than quantity. Spectrum of alcoholic liver disease included fatty liver, alcoholic hepatitis and cirrhosis. Fatty liver, transient and reversible, is seen in any individual consuming a large quantity of alcohol over a long period of time [1]. Only 15-20% of chronic heavy drinkers develop hepatitis or cirrhosis occurring concomitantly or in succession [2]. Amount of alcohol intake at risk for alcoholic hepatitis is not known, but the majorities have a history of heavy alcohol consumption more than 100 g/day for more than two decades [3].

Chronic liver disease is an advance disease process lasting more than six months that involves progressive destruction and regeneration of the liver parenchyma ultimately leading to fibrosis and cirrhosis. It comprises of a wide range of liver pathologies, which include inflammation, liver cirrhosis, and hepatocellular carcinoma. Patients usually present with complications of chronic liver disease including portal hypertension, hepatic encephalopathy, hepatorenal syndrome, hepatopulmonary syndrome, portopulmonary hypertension, cirrhotic cardiomyopathy and malnutrition. Portal hypertension is an important complicating feature of decompensated cirrhosis, which is responsible for the development of ascites, spleenomegaly and gastro-esophageal varices. Portal hypertension is defined as a hepatic venous pressure gradient (HVPG) of ≥ 5 mmHg. Acute haemorrhage from ruptured gastroesophageal varices is a medical emergency that occurs when HVPG exceeds 12mmHg and above 20mmHg failure to control bleeding hence increased mortality [4]. Determining HVPG is an invasive procedure where a catheter passed under radiological guidance into the hepatic vein where free and wedged hepatic pressures are measured, the gradient of wedged and free pressure give HVPG. Moreover direct visualization of gastro-esophageal varices itself is an invasive procedure.

Around 50% of patient with portal hypertension develops varices and bleeding varices depends on the size. Mortality from acute variceal bleeding is as high as 20% even with the recent improvement in diagnosis and management [5]. Moreover, it is the second most common cause of death in cirrhotic patients [6,7]. Predicting gastro-esophageal varices without intervention is a tedious task. In case of medical emergency of upper gastrointestinal bleeding, identifying etiology of bleeding to be esophageal varix without prior history and invasive procedure is cumbersome. Just less than 50% of cirrhotic patients do have varices at diagnosis. Management and prognosis of variceal bleeding is entirely different and also re-bleeding is common ~ 30%-50% [5].Few non-invasive measure like splenomegaly, increased portal vein diameters on ographically, decreased platelet count etc. can predict varices (esophageal) but not with precision. This study is conducted in order to see the relationship of these non-invasive measures with the occurrence of varices and its bleeding tendency.

Identifying non-invasive measure of varices prediction and bleeding tendency can be advantageous in the country like ours as invasive modalities are limited to urban areas. In our country where most of the variceal bleedings are managed conservatively due to lack of facilities, this would add ease to complexity. Moreover, prophylactic use of non-selective beta-blockers can be done using non-invasive predictors in chronic liver disease patients.

Materials and Methods

This study is a prospective cross-sectional study done is Nobel Medical College and Teaching Hospital, Biratnagar from September 2018 to August 2019. This study was started after acquiring approval from the Institutional Review Committee of Nobel Medical College. Written consent was acquired after the patient or patient party was explained about the study, its advantages, procedures and disadvantages. Patients presented to Nobel Hospital within the time frame with history of chronic ethanol ingestion and features suggestive of chronic liver disease clinically and investigation wise were enrolled in the study. Patient falling under the spectrum of chronic hepatitis and cirrhosis were taken. In the study done by Bhattarai S [12], platelet count < 1,44,000/cumm as non-invasive

predictor of oesophageal varices has 87.9% sensitivity. Using $n=z^2pq/d^2$ with 10% error, sample size is calculated to be 53. Total number of patient taken into studied was 100.Relevant history, physical examination along with platelet count, prothrombin time was taken on the day of admission. Patient in the study underwent ultrasonography and upper gastrointestinal endoscopy on subsequent days to see the splenic diameter, and varices grading and bleeding spots respectively. Data collected was entered in MS Excel and SPSS 23.0. Mean, median, standard deviation; Pearson's chi-square test, Multivariate analysis of variance (MANOVA), ROC curve etc. was analyzed using SPSS 23.0.

Results

Total number of patients included in the study was 100, 76% were male and 24% female. Mean age of the study population was 53.41 years (median 52 years) ranging from 33 to 75 years. Esophageal varices were present in 53 (53%) patients and of them 23 had grade 1 varices, 22 had grade 2 and 8 had grade 3 varices. The demographic characteristics of the 100 patients included in the study are shown in Table 1.whereas, main clinical and biochemical characteristics of the study population is shown in Table 2.

Table 1: Gender wise distribution

Gender	Number	Percentage
Male	76	76%
Female	24	24%

Table 2: Main clinical and biochemical characteristics of the study population.

Predictors	Unit	Mean	Median	Range
Age	years	53.41	52.0	33-75
Platelet count	n/mm^3	157460	159000	60000-395000
Spleen diameter	mm	120.4	120.7	70-165
PT	sec	17.6	16.9	12-45
Platelet/spleen diameter	n/mm^3/mm	1392.5	1199.3	462.7-3722.2

In the study, varices was seen in 37 (48.7%) males and in 16 (66.7%) females. Mean age of patient with and without varices was 52.5 years and 54.5 years respectively. Mean age of male with varices was 52.9 years whereas female was 51.4 years.

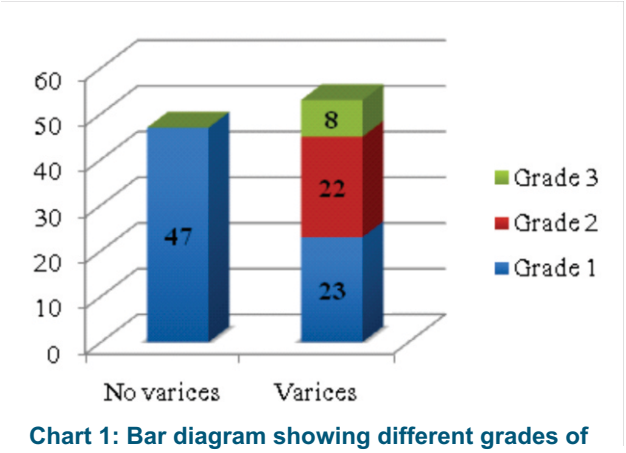

Chart 1: Bar diagram showing different grades of esophageal varices

Patients with varices had mean platelet count 122566±36024.8 /mm^3, mean splenic diameter 133.1±21.3 mm, mean prothrom- bin time (PT) 19.3±5.0 sec and mean ratio of platelet per spleen diameter 930.2 ± 259.4 /mm^3/mm.

Table 3: Means ± SD of different predictors of study patients in relation to presence or absence of esophageal varices.

Predictors	Unit	Varices	No-varices
Age	years	52.5±10.7	54.5±11.2
Platelet count	n/mm	122566.0±36024.8	196808.5±58202.3
Spleen diameter	mm	133.1±21.3	106.1±19.7
PT	sec	19.3±5.0	15.7±3.1
Platelet/spleen diameter	n/mm^3/mm	930.2±259.4	1931.9±626.0

Similarly in patient with grade 3 varicesmean platelet count was 119500 ± 31341.4 /mm^3, mean spleen diameter was 141.4 ± 23.7 mm and mean PT was 23.6 ± 9.4 sec.Mean ratio of platelet count per splenic diameter was 862.2 ± 235.8 /mm^3/mm.

Table 4: Co-relation between different predictors and severity of varices.

Predictors	Unit	Grade 1	Grade 2	Grade 3
Age	years	53.1±9.9	50.7±9.7	55.8±15.2
Platelet count	n/mm^3	120565.2±33758.3	12577.2±40908.6	119500 ± 31341.4
Spleen diameter	mm	130.0±21.0	133.0 ± 20.8	141.4 ± 23.7
PT	sec	18.2±3.9	18.9±2.8	23.8 ± 9.3
Platelet/spleen diameter	n/mm^3/mm	935.1±253.6	949.8±280.2	862.2 ± 678.9

Features suggestive of variceal bleeding was seen in patients with mean platelets counts of 119843.8±34062.7 /mm^3, mean PT of 19.6±5.6 sec and mean platelet per spleen diameter ratio of 878.5±251.2 /mm^3/mm. 100% of grade 3 oesophageal varices had features of recent bleeding.

Table 5: Predictors of variceal bleeding

Predictors	Unit	Variceal bleeding
Platelet count	n/mm^3	119843.8 ±34062.
PT	sec	19.6 ±5.6
Platelet/spleen diameter	n/mm^3/mm	878.5 ±253.6
Oesophagealvarices	Grade 3	100%

Sensitivity and specificity of platelets count less than 150000/mm^3 in predicting varieswas71.7% and 83.0% respectively, with splenic diameter more than 123.3 mm was75.5% and 83.0% respectively. Moreover PT more than 16.6 sec has sensitivity and specificity of predictingvarices 71.7% and 63.8% respectively. Similarly platelet per splenic diameter ratio cutoff 1293.7 has 88.7% sensitivity and 85.1% specificity for predicting varices.

If predictive value of platelets count for varices was taken to less than 163500/mm^3 then sensitivity and specificity was83.0% and 83.0% respectively. Another ratio of platelet count per splenic diameter per prothrombin time was also calculated. (Platelet/splenic diameter)/PT /mm^3/mm/seccutoff value of83 has specificity and sensitivity of 96.2% and 83.0% respectively in predicting the varices.

Table 6: Sensitivity, specificity, positive & negative predictive values and p values of different non-invasive predictors of varices at cut off values

Predictor	Value/Unit (cut off)	Sensitivity	Specificity	Positive predictive value	Negative predictive value	p
Platelets	1,50,000/mm^3	71.7%	83.0%	82.6%	72.2%	<0.001
	1,63,500/mm^3	83.0%	83.0%	84.6%	81.3%	<0.001
Splenic diameter	123.3 mm	75.5%	83.0%	83.3%	75.0%	<0.001
PT	16.6 sec	71.7%	63.8%	69.1%	66.7%	<0.001
Platelet per splenic diameter (Platelet per splenic diameter) per PT	1293.7/mm^3/mm	88.7%	85.1%	87.0%	87.0%	<0.001
	83/mm^3/mm/sec	96.2%	83.0%	86.4%	95.1%	<0.001

Discussion

Variceal hemorrhage is a devastating complication of chronic liver disease. The mortality of first episode of acute variceal bleeding was 30%, which increased on subsequent bleeding episode before widespread use of current therapies, and only one-third of patients survived for one year [8,9]. UGI

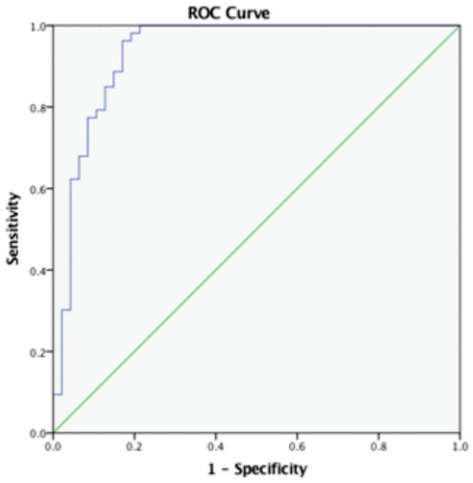

Figure 1: ROC curve for Platelet per spleenic diameter (AUC - 0.935)

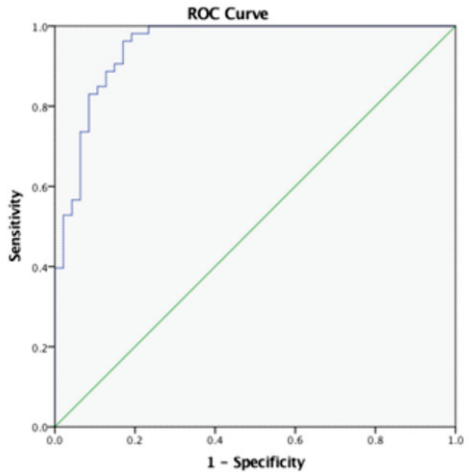

Figure 2: ROC curve for Platelet per splenic diameter per PT (AUC- 0.949)

Endoscopy is regarded as the best screening modality for diagnosing varices and the presence of large varices, cherry red spots etc. on endoscopy are high risk signs associated with bleeding [10,11]. Endoscopic surveillance for varices is recommended for cirrhotic patient repeatedly. UGI endoscopy is an invasive modality that is not accepted by patient at their ease. Moreover availability of this invasive test in rural areas of developing country like ours where chronic alcoholism and chronic liver disease is a common condition is scarce. Many non-invasive predictors of oesophageal varices are studied in different study of which few reliably available modalities are studied in this study.

Of 100 patients studied in the study 76 (76%) were male, similar male predominance of 77%, 69.3% and 86.1% was observed in studies carried out by Bhattarai S et al [12] Mandal L et al [13] and Sharma SK et al [14] respectively. Median age of study population was 52 years which reported similar 54 years as in the study carried out by Bhattrai et al [12] whereas the age was higher in the other above studies 40 and 45 years respectively.

Oesophageal varices were detected in 53% of the patients, in contrary higher number of varices were detected in other studies carried out by Bhattrai et al [12] and Mandal L et al [13] 70% and 75.6% respectively. The difference was mainly due to the study population, which not only included cirrhotic but chronic alcolohic liver disease as a whole. Almost equal numbers of patients have grade 1 and 2 oesophageal varices 23 and 22 respectively whereas only 8 have grade 3.

Average platelet count with and without varices was 122566.0±36024.8/cumm and 196808.5 ± 58202.3/cumm respectively. Amongst the different varices platelet count were 120565.2 ± 33758.3/cumm, 12577.2 ± 40908.6/cumm and 119500 ± 31341.4/cumm in Grade 1, 2 and 3 varices respectively. Similar results with average platelet counts with and without varices wasobserved 111890 ± 3584/cumm and 176570 ± 7510/cumm respectively in the study by Bhattrai et al [12]. Another study by Mandal et al [13] also had lower platelet count with varices111000± 2840/cumm whereas platelet count was 215000 ± 5500/cumm without varices, which was higher then above studies. Taking cutoff limit of platelet count <150000/cumm for presence of varices, the sensitivity and specificity was 71.7% and 83% respectively. In other studies, Shanker et al [15] reported platelet count of <120000/cumm to be 90% sensitive and 50% specific in predicting oesophagealvarices. Similarly, Thomopoulos et al [16] mentioned platelet count of <118000/cumm to be a good indicator for presence of varices with sensitivity of 95% and specificity of 73%. In Bhattrai et al [12] study sensitivity of 87.9 % and specificity of 41.7% for cutoff platelets count of <144000/cumm was observed. Though lower platelet count had higher sensitivity in predicting varices but lacked specificity.

Average splenic diameter of 133.1 ± 21.3mm was observed in patients with varices, whereas 106.1 ± 19.7mm in without varices. In the study by Bhattrai et al [12] average spleen size with varices was 155.0± 0.10mm and without varices was 126.6± 21.5mm. Mandal et al [13] study found that average spleen size for patients with varices as 149.9 ± 19.2mm and without varices as 131.3± 11.0mm. Shanker et al [15] reported similar findings that average size of spleen in variceal group 146.9±10.8 mm was larger than in non-variceal group 124.5±6.50mm. The cutoff value of splenic diameter of 123.3mm (by ROC curve) was 75.5% sensitive and 83% specific in identifying varices. Spleen size >139mm had 97.1% sensitivity and 76.7% specificity for prediction for varices in Bhattrai et al [12]study whereas, Shanker et al [15] reported 90% sensitivity and 80% specificity when the spleen size was >135 mm which were higher than our study mainly due to the study population that didn't consist of patient in end-stage chronic liver disease.

The average platelet count per splenic diameter ratio was 930.2 ± 259.4 in patients with varices and 1931.9 ± 626.0 in patients without varices. The sensitivity and specificity of the ratio cutoff value 88.7% and 85.1% respectively when cutoff value was taken less than 1293.7 (by ROC curve). In the study done by Giannini et al [17] the cut off value for platelet to splenic diameter ratio 909 had sensitivity 100% and specificity 93%.Platelet count per spleen ratio had AUC= 0.935 and cutoff value less than 1293.7 with p value <0.001 is excellent predictor of varices in patient with chronic alcoholic liver disease which was also excellent predictor shown in study carried out by Giannini et al [17] and Zimbwa et al [18]. But the cutoff value of the ratio was taken 909 in both the studies and the later study showed 100% specificity as well.

Another ratio calculated in this study was platelet count per splenic diameter per prothrombin time ratio whose cutoff value 83 (according to ROC curve) was 96.2% sensitive and 83.0% specific in predicting varices. AUC as per ROC curve was 0.949 with p value <0.001 shows the ratio is an excellent test to predict occurrence of varices.

Variceal bleeding was seen higher in patients with low platelet count (mean 119843.8 ± 34062.7), high PT (mean 19.6 ± 5.6), low platelet per spleen diameter (mean 878.5 ± 253.6) and grade 3 varices (100%) with p value <0.001.

Conclusion

In chronic alcoholic liver disease patient low platelet count, increased spleen diameter, low platelet per spleen diameter ratio and low platelet per spleen diameter per PT ratio are useful in predicting presence of oesophageal varices. Amongst these both the ratios platelet per splenic diameter and platelet per splenic diameter per PT ratio are excellent tools to predict varices. Thus non-invasive predictors mentioned above can be

greater tool in differentiating patient with or without varices where invasive modalities are not available.

References

[1] O'Shea RS, Dasarathy S, Mc Cullough AJ, Alcoholic liver disease, Hepatology.51:1 (2010) 307-328.DOI: 10.1002/hep.23258.

[2] Menon KVN, Gores GJ, Shah VH, Pathogenesis, diagnosis and treatment of alcoholic liver disease, Mayo Clinic Proceedings.76:10 (2001)1021-1029.DOI: 10.4065/76.10.1021.

[3] Naveau S, Giraud V, Borotto E,Aubert A, Capron F, Chaput JC, Excess weight risk factor for alcoholic liver disease, Hepatology. 25 (1997) 108.DOI: 10.1002/hep.510250120.

[4] Burroughs AK, Triantos CK, Predicting failure to control bleeding and mortality in acute variceal bleeding, J Hepatol.48:2 (2008) 185–8. DOI: 10.1016 / j.jhep.2007.11.006.

[5] Escorsell A, Pavel O, Cárdenas A, Morillas R, Llop E, Villanueva C, et al, Esophageal balloon tamponade versus esophageal stent in controllong acute reftractory variceal bleeding: a multicentreran-domised controlled trial, Hepatology. 63:6 (2016) 1957–67.DOI: 10.1002/hep.28360.

[6] Carbonell N, Pauwels A, Serfaty L, Fourdan O, Levy VG, Poupon R, Improved survival after variceal bleeding in patients with cirrhosis over the past two decades, Hepatology. 40:3 (2004) 652–9.DOI: 10.1002/hep.20339.

[7] Garcia-Tsao G, Sanyal AJ, Grace ND, Carey W, Practice Guidelines Committee of the American Association for the Study of Liver Diseases; Practice Parameters Committee of the American College of Gastroenterology, Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis, Hepatology. 46:3 (2007) 922–38.DOI: 10.1002/hep.21907.

[8] Smith JL, Graham DY, Variceal hemorrhage: a critical evaluation of survival analysis. Gastroenterology. 82:5 (1982) 968.PMID: 7037525.

[9] Graham DY, Smith JL, The course of patients after variceal hemorrhage. Gastroenterology. 80:4 (1981) 800.PMID: 6970703.

[10] Jensen DM, Endoscopic screening for varices in cirrhosis: findings, implications, and outcomes, Gastroenterology. 122:6 (2002) 1620-30.DOI: 10.1053/gast.2002.33419.

[11] D'Amico G, Garcia-Tsao G, Pagliaro L, Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies, J Hepatol. 44:1 (2006)217–31.DOI: 10.1016/j.jhep.2005.10.013.

[12] Bhattarai S, Dewan KR, Shrestha G, Patowary BS. Non-Invasive Predictors of Gastro-Oesophageal Varices, JNMA J Nepal Med Assoc. 56:207 (2017)298-303.PMID: 29255309.

[13] Mandal L, Mandal SK, Bandyopdhyay D, Datta S, Correlation of portal vein diameter and splenic size with gastro-esophageal varices in cirrhosis of liver. JIACM. 12:4 (2011)266-70.

[14] Sharma SK, Aggarwal R, Prediction of large oesopha-gealvarices in patients with cirrhosis of the liver using clinical, laboratory and imaging parameters. Journal of Gastroenterology and Hepatology.22:11 (2007)1909-15.DOI: 10.1111/j.1440-1746. 2006. 04501.x

[15] Shanker R, Banerjee S, Anshul, Ganguly S, Bansal S, Uppal A, et al., A study of association of portal vein diameter and splenic size with gastrooesopha-gealvarices in liver cirrhosis patients, IOSR Journal of Dental and Medical Sciences.15:9 (2016)125-9.DOI: 10.9790/0853-150906125129.

[16] Thomopoulos KC, Labropoulou-Karatza C, Mimidis KP, Katsakoulis EC, Iconomou G, Nikolopoulou VN, Non-invasive predictors of the presence of large oesophagealvarices in patients with cirrhosis, Dig Liver Dis. 35:7 (2003) 473-8.DOI: 10.9790/0853-150906125129.

[17] Giannini E, Botta F, Borro P, Risso D, Romagnoli P, Fasoli A, et al., Platelet count/spleen diameter ratio: proposal and validation of a non-invasive parameter to predict the presence of oesophageal varices in patients with liver cirrhosis, Gut. 52:8 (2003)1200-1205.DOI: 10.1136/gut.52.8.1200.

[18] Zimbwa TA, Blanshard C, Subramaniam A, Platelet count/spleen diameter ratio as a predictor of oesophagealvarices in alcoholic cirrhosis. Gut. 53:7 (2004) 1055.PMID: 15194662.