A comparative study between three noninvasive predictors of oesophageal varices in post hepatitis C virus liver cirrhosis in Egypt

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Abstract

Background and aim : **The prevention of variceal bleeding is very important. The current guide lines recommend screening of all cirrhotic patients by endoscopy, to identify patients at risk of bleeding in whom prophylactic treatment should be started. Repeated endoscopic examinations are unpleasant for patients, and carry a high cost impact and burden on endoscopic units, while only 50% of cirrhotic patients have esophageal varices, 30% of whom have large varices. *The aim* of this study is to evaluate prospectively the spleen size, platelet count and platelet count/spleen diameter ratio as noninvasive predictors of oesophageal varices in post hepatitis C virus liver cirrhosis in Egypt.**

Patients and methods : **One hundred patients with post hepatitis C virus liver cirrhosis were included in the study. All studied subjects underwent a detailed history taking, clinical examination, biochemical workup, upper gastrointestinal endoscopy and abdominal ultrasound. The platelet count to spleen diameter ratio was calculated.**

Results : **All the 3 predictors showed high statistically significant correlation with the presence, size and the grade of oesophageal varices ($P < 0.01$). Among the 3 noninvasive predictors the platelet count/spleen diameter ratio gave the highest accuracy (94%) at a cut-off value of 1326.58 followed by the spleen size (89%) at a cut-off value of 131.5 mm and lastly the platelet count (84%) at a cut-of value of 131000/mm^3.**

Conclusion : **The use of the three studied predictors in this study can help the physicians to restrict endoscopy to those who are highly suspected to have oesophageal varices.** (Acta gastroenterol. belg., **2011**, 74, **497-502**).

Key words : noninvasive predictors of oesophageal varices, the platelet count/spleen diameter ratio, oesophageal varices, portal hypertension, post HCV liver cirrhosis.

Introduction

Egypt has a very high prevalence of hepatitis C virus (HCV) and a high morbidity and mortality from chronic liver disease (1). HCV is considered the most common aetiology of chronic liver disease in Egypt, where the prevalence of antibodies to HCV (anti-HCV) is 10-fold greater than in the United States and Europe (2).

Portal hypertension is a major complication of liver cirrhosis, and leads to the development of portosystemic shunts. Oesophageal varices are the most important among these shunts due to its clinical effects and play a major role in transforming the disease from a pre-clinical to a clinical phase. Longitudinal studies have shown that oesophageal and/or gastric varices eventually develop in all cirrhotic patients (3,4) and that once they have developed they tend to increase in size and to bleed (4). The yearly rate of development of new varices is about 5-10% (3,5) ; the rate of growth of varices from small to large ranges between 5% and 30% in different studies (5-8). Bleeding from oesophageal varices is the most serious complication of cirrhosis, with a high risk of death (9). The mortality from each episode of variceal bleeding is 17%-57% (4,10,11). On endoscopic examination the presence of red spots on the varices equals high risk of bleeding which is also related to the size of varices (12,13).

The prevention of variceal bleeding is very important and non-selective beta blockers and/or prophylactic band ligation decrease the risk of bleeding by 50% (14,15). It is recommended that all cirrhotic patients should undergo endoscopic screening for the presence of varices (16-21), patients who have large or medium sized varices should be treated to prevent bleeding.

Patients with compensated cirrhosis who do not have varices should repeat endoscopy every 2-3 years, and every 1-2 years for those with small varices (17). It is also recommended for patients with decompensated cirrhosis to repeat endoscopy every year even if there are no varices (17,19). Repeated endoscopic examinations are unpleasant for patients, and carry a high cost impact and burden on endoscopic units, while only 50% of cirrhotic patients have esophageal varices, and up to 30% have large varices. For these reasons many non-invasive predictors for the presence and size of varices have been studied.

This study attempts to evaluate prospectively the spleen size, platelet count and platelet count/spleen diameter ratio as noninvasive predictors of oesophageal varices in post hepatitis C virus liver cirrhosis in Egypt.

Materials and methods

This prospective study included one hundred patients with post hepatitis C virus liver cirrhosis who were under investigations and treatment at the Gastroenterology & Hepatology outpatient clinics or those who were

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admitted to the Internal Medicine departments of the Cairo university hospitals.

Diagnosis of cirrhosis was based on physical findings, laboratory investigations and imaging findings. Patients who previously underwent injection sclerotherapy, band ligation, surgery for oesophageal varices, or who had previous or active gastrointestinal bleeding and those who were receiving beta blockers were excluded from the study. All patients with liver cirrhosis due to causes other than HCV were also excluded. Also patients with concomitant hepatic schistomiasis were excluded (N = 7).

All studied subjects underwent a detailed history taking, clinical examination and a biochemical workup, including total bilirubin, aspartate aminotransferase, alanine aminotransferase, serum albumin, prothrombin activity, complete blood count and viral markers for hepatitis C and hepatitis B viruses. Child-Pugh score was calculated for all patients using the 5 parameters (ascites, albumin, bilirubin, prothrombin activity and encephalopathy) (22). An upper gastrointestinal endoscopy and abdominal ultrasound were performed in all patients.

The maximum spleen bipolar diameter was measured and the values were recorded. The platelet count to spleen diameter ratio was calculated.

All endoscopies were performed in a single endoscopy unit by an experienced endoscopist and a grading classification I-IV was used (23). Grade I was used for varices in the level of mucosa, grade II for varices smaller than 5 mm filling less than 1/3 of the oesophageal lumen, grade III for varices larger than 5 mm filling more than 1/3 of the oesophageal lumen and grade IV for varices occupied more than 2/3 of esophageal lumen. Informed consent was obtained from all patents in the study. All the data were recorded, analyzed and correlated.

Data were statistically described in terms of range, mean ± standard deviation (± SD), median, frequencies (number of cases) and percentages when appropriate. Comparison of quantitative variables between the study groups was done using Mann Whitney *U* test for independent samples when comparing 2 groups and Kruskal Wallis analysis of variance (ANOVA) test with Mann Whitney *U* test for independent samples as posthoc multiple 2-group comparisons when comparing more than 2 groups. For comparing categorical data, Chi square (χ^2) test was performed. Exact test was used instead when the expected frequency is less than 5. Accuracy was represented using the terms sensitivity, specificity, +ve predictive value, -ve predictive value, overall accuracy, the likelihood ratio of a positive test and the likelihood ratio of a negative test. Receiver operator characteristic (ROC) analysis was used to determine the optimum cut off value for the studied diagnostic markers. A probability value (*p* value) less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs Microsoft Excel 2007 (Microsoft Corporation, NY, USA) and SPSS (Statistical Package for the Social Science ; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

Results

48 men and 52 women were included in the study, all with post HCV liver cirrhosis. The main clinical characteristics of all patients are shown in table 1.

The mean values of platelet (PLT) count, spleen diameter and PLT count/spleen diameter ratio showed a highly significant association with the presence, grade and size of varices as shown in table 2 A, table 2B and table 3.

The sensitivity, specificity and accuracy of PLT count, spleen diameter and PLT count/spleen diameter ratio as noninvasive predictors of oesophageal varices were studied by applying the ROC curve to detect the cut off values with the best sensitivity and specificity.

Among the three noninvasive predictors the platelet count/spleen diameter ratio gave the highest accuracy (94%) at a cut-off value of 1326.6 followed by the spleen size at a cut-off value of 131.5mm and lastly the platelet count at a cut-of value of 131000/mm^3 as shown in table 4 and figures 1-3.

When we applied the same cut of value of 909 used by Giannini for the platelet count/spleen diameter ratio on the current study, the accuracy was significantly reduced (84%) as shown in table 4.

The cut off values with the best sensitivity and specificity of the three predictors regarding the detection of the large varices were also studied by applying the ROC curves. The platelet count/spleen diameter ratio gave the highest accuracy (84%) among the three predictors as shown in table 4.

The performance of the three parameters as noninvasive predictors of oesophageal varices in patients with Child class A (N = 20) was studied. Seven out of 20 had small varices and 13 had no varices. There was a significant association between the mean values of the three parameters and the presence of varices (table 5A). The best cuts off values of the three predictors regarding the presence of varices were also studied by applying the ROC curves. The platelet count/spleen diameter ratio showed the highest accuracy (90%) at a cut off value of 1574 (Table 5B).

Discussion

Bleeding oesophageal varices is still a leading cause of death in patients with cirrhosis. In recent studies, mortality rates vary between 11% and 20% within six weeks of the bleeding episode (24-27).

Endoscopy is still the gold standard method for diagnosis of oesophageal varices and is recommended every two to three years in cirrhotic patients without varices, and every one to two years in patients with small varices (14,28,29). Several studies have been performed to find noninvasive parameters that can predict the

Table 1. — **Showing the patients clinical characteristics**

Main clinical characteristics of all patients	
Total number	100
Gender (M/F)	48/52
Age (mean ± SD)	49.2 ± 8
Age (range)	20-70
Child class (A/B/C)	20/31/49
Varices present (yes/no)	82/18
Grade of varices (I/II/III/IV)	7/15/35/25
Varices size (Small /large)	22/60
Mean Hemoglobin concentration, gm/dl (mean ± SD)	10 ± 1
Mean PLT count, mm^3 (mean ± SD)	117070 ± 66145.9
Mean spleen diameter, mm (mean ± SD)	150.9 ± 23.4
Mean PLT count/spleen ratio (mean ± SD)	843.3 ± 616.3
Mean albumin concentration, gm/dl (mean ± SD)	2.6 ± 0.6
Mean bilirubin level mg/dl (mean ± SD)	2.1 ± 3.2
Mean prothrombin conc % (mean ± SD)	58% ± 0.2%

Table 2A. — **Comparison between all parameters with and without varices**

Predictor	Varices present	Varices not present	P value
PLT count, mm^3 (mean ± SD)	95,561 ± 41,519.9	215,055.6 ± 69,772.3	< 0.001
Spleen diameter, mm (mean ± SD)	157.4 ± 19.7	121.2 ± 13.6	< 0.001
PLT count/spleen ratio (mean ± SD)	624.8 ± 301.4	1838.4 ± 707.2	< 0.001

Table 2B. — **Comparison between all parameters with small and large varices**

Predictor (mean ± SD)	Small varices	Large varices	P value
PLT count (mm^3)	121090.9 ± 54686.9	86200 ± 31146.3	< 0.01
Spleen diameter (mm)	145.6 ± 17.1	161.8 ± 19	< 0.002
PLT count/spleen ratio	839.1 ± 379.2	546.2 ± 223.9	< 0.002

presence of oesophageal varices in liver cirrhosis to reduce the cost and burden on endoscopy units (28).

The prevention of bleeding from oesophageal varices is an important goal. Identification of patients who are at risk of variceal bleeding is the first step in prevention of bleeding so the patients can be selected to start prophylactic treatment.

The prevalence of oesophageal varices among cirrhotics is variable, ranging from 24% to 80% (30). The value of diagnosing oesophageal varices by a noninvasive predictor is to target endoscopy to patients who have a high probability of having varices.

In the present study as shown in tables 2-4 and figures 1 and 2 and like in many other previous studies (31-37) platelet count and spleen diameter correlate well with the presence of oesophageal varices. However, in cirrhotic patients, the presence of thrombocytopenia may be due to several factors other than portal hypertension, as shortened mean platelet lifetime, decreased thrombopoietin production or myelotoxiceffects of the hepatitis C virus (38). The presence of splenomegaly in cirrhotic patients is mainly related to portal hypertension.

In 2003 Giannini *et al.* (28) introduced the use of the platelet count/spleen diameter ratio as a predictor of oesophageal varices. This ratio links thrombocytopenia to splenomegaly to introduce a variable that takes into consideration that thrombocytopenia is mainly due to hyperslenism secondary to portal hypertension. In his study with a cut-off value of 909 the sensitivity was 100% and the specificity was 93%. In 2006 Giannini *et al.* (39) reported the results of a multicenter study to validate the use of platelet count/spleen diameter ratio in the prediction of oesophageal varices at cut-off value of 909 which showed that the sensitivity was 92% and specificity was 67%. Many studies (23,39-42) have been performed using different best cut-off values to investigate this parameter as a noninvasive predictor for oesophageal varices. The differences of the positive predictive value and negative predictive value between this study and the other studies can be explained by different factors affecting the platelet count including : bleeding, infection, medications and lower thrombopoetin levels in cirrhosis etc. In addition to these factors both ultrasounds and endoscopy are operator dependent techniques and the lack of interobserver agreement between the operators of the different studies may greatly affect the results. In the present study the best cut-off value was 1326.6 for the platelet count/spleen diameter ratio which showed 96.3% sensitivity and 83.3% specificity as shown in table 4 and figure 3.

In conclusion, as mentioned in the introduction, most current guidelines recommend that all cirrhotic patients

Table 3. — **Correlation between all predictors and grades of varices**

Predictor (mean ± SD)	Oesophageal varices grade				P value
	I	II	III	IIII	
PLT count (mm^3)	167,428.6 ± 59,969	99,466.7 ± 37,015.2	96,000 ± 31,167.5	72,480 ± 25,932.8	< 0.001
Spleen diameter (mm)	136.3 ± 16	149.9 ± 16.3	160.6 ± 14.1	163.5 ± 24.4	< 0.007
PLT count/ spleen ratio	1204.3 ± 364.6	668.8 ± 247	600 ± 199.6	470.9 ± 237.9	< 0.001

Table 4. — **Comparison between the accuracy of the three parameters in predicting the presence of oesophageal varices and in detecting large varices**

Predictor	AUROC	Cut off point	Sensitivity (%)	Specificity (%)	(+)ve PV(%)	(-)ve PV(%)	Accuracy (%)	LR+	LR-
PLT count in predicting presence of varices	0.912	131000	84.2	83.3	95.8	53.6	84	5.1	0.2
PLT count in predicting large varices	0.676	93500	69.5	55.6	87.7	28.6	67	1.56	0.55
Spleen size in predicting presence of varices	0.934	131.5	90.2	83.3	96.1	65.2	89	5.4	0.1
Spleen size in predicting large varices	0.728	153	72	66.7	90.8	34.3	71	2.16	0.42
PLT count/spleen ratio in predicting presence of varices	0.927	1326.6	96.3	83.3	96.3	83.3	94	5.8	0.0
PLT count/spleen ratio using (Giannini cut off 909)*	0.927	909	84.2	83.3	95.8	53.6	84.00	5.1	0.2
PLT count/spleen ratio in predicting large varices	0.727	913.2	94	40.9	87.5	58.3	84	1.54	0.16

* The accuracy of plt count/spleen ratio in predicting the presence of varices by applying the same cut off value (909) Giannini used on the current study.

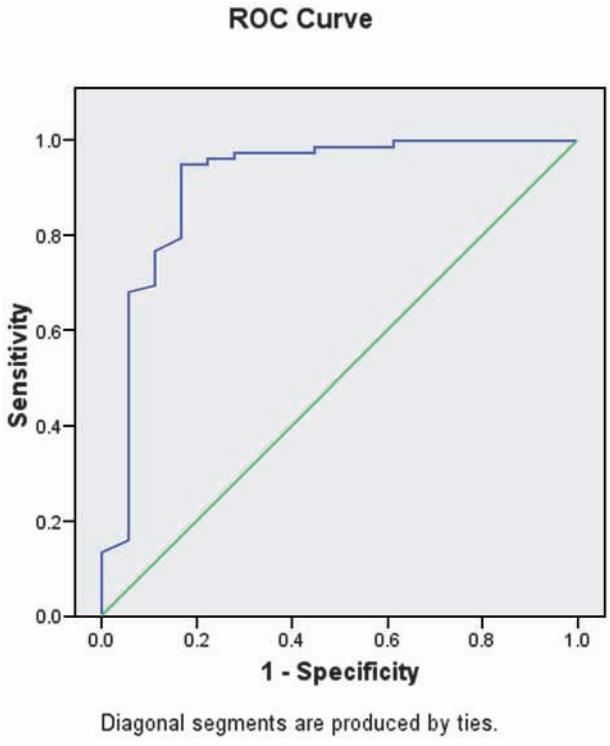

Fig. 1. — ROC curve for sensitivity and specificity of platelet count for the prediction of varices.

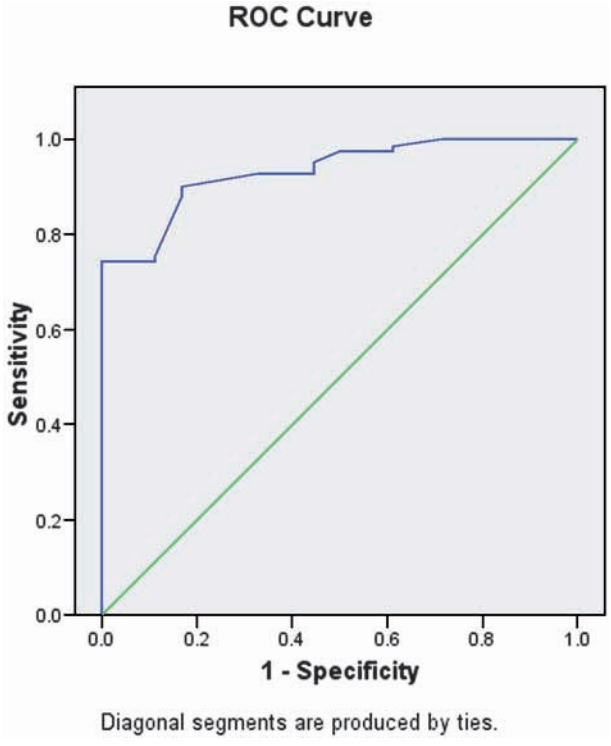

Fig. 2. — ROC curve for sensitivity and specificity of spleen size for the prediction of varices.

Table 5A. — **Comparison between all parameters with and without varices among patients with child class A**

Predictor	Varices present (N = 7)	Varices not present (N = 13)	P value
PLT count, mm^3 (mean ± SD)	181000 ± 43324.4	229153.8 ± 61377	< 0.05
Spleen diameter, mm (mean ± SD)	146.6 ± 10.9	116.7 ± 12.4	< 0.001
PLT count/spleen ratio (mean ± SD)	1240.1 ± 314.6	2014.8 ± 649	< 0.005

Table 5B. — **Comparison between the accuracy of the three parameters in predicting the presence of oesophageal varices among patients with child class A**

Predictor	AUROC	Cutoff value	Sensitivity (%)	Specificity (%)	(+)ve PV(%)	(-)ve PV(%)	Accuracy (%)	LR+	LR-
PLT count in predicting varices	0.774	221000	85.7	53.8	50	87.5	65	1.86	0.27
Spleen size in predicting varices	0.89	125	100	76.9	70	100	85	4.33	0
PLT count/spleen ratio in predicting varices	0.956	1574	100	84.6	77.8	100	90	6.5	0

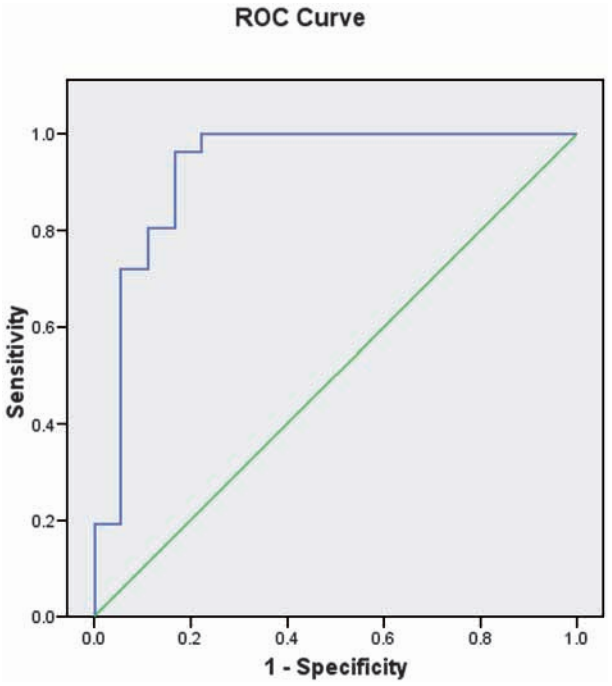

Fig. 3. — ROC curve for sensitivity and specificity of platelet count/spleen diameter ratio for the prediction of varices.

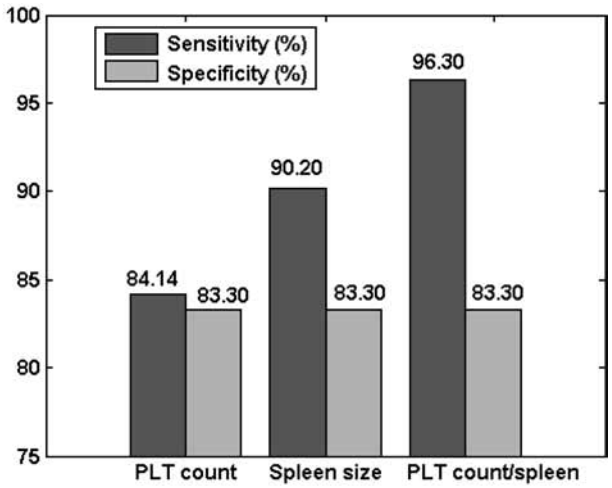

Fig. 4. — Comparison between sensitivity & specificity of the three parameters in predicting the presence of oesophageal varices of varices.

should be screened by upper gastrointestinal endoscopy for the presence of oesophageal varices at the time of diagnosis. Endoscopy is recommended every two to three years in patients without varices, and follow up endoscopy is recommended every one to two years in patients with small varices.

Of course endoscopy still is the gold standard for the diagnosis of oesophageal varices. However, the platelet count to spleen diameter ratio may be a useful method for noninvasive prediction of oesophageal varices especially in Egypt where resources are limited and endoscopic facilities are not available in all areas, to select the patients likely to have oesophageal varices so they can be referred to other centers where such facilities are available. This also can be used to rearrange the long waiting lists in the endoscopic units, reduce the number of endoscopies in patients with post hepatitis C virus liver cirrhosis and target endoscopy to those at high risk of varices presence in Egypt.

Although argues against the accuracy of noninvasive predictors of oesophageal varices is still going, in this study we found that platelet count/spleen diameter ratio, spleen size and platelet count are noninvasive predictors for the presence of oesophageal varices with a good degree of accuracy specially the Platelet count/spleen diameter ratio. The use of the three studied predictors in this study can help the physicians to restrict endoscopy to

those who are highly suspected to have oesophageal varices to start the prophylactic therapy and not to use the endoscopy for all the patients.

Among the noninvasive parameters studied in this study, the platelet count/spleen diameter ratio had the highest accuracy for diagnosing oesophageal varices (sensitivity 96.3% and specificity 83.3%). More studies are required on a larger sample of post hepatitis C cirrhosis patients for final validation of platelet count/spleen diameter ratio in Egypt and to determine a cut-off value that can be safely recommended for the noninvasive diagnosis oesophageal varices.

References

1. LAVANCHY D., MC MAHON B. Worldwide prevalence and prevention of hepatitis C. *In* : LIANG T.J., HOOFNAGLE J.H. (eds). Hepatitis C. San Diego, Academic Press, 2000 : 185-202.
2. STRICKLAND G.T., ELHEFNI H., SALMAN T., WAKED I., ABDEL-HAMID M., MIKHAIL N., ESMAT G., FIX A. Role of hepatitis C infection in chronic liver disease in Egypt. *Am. J. Trop. Med. Hyg.*, 2002, **6** : 436-442.
3. CHRISTENSEN E., FAUERHOLDT L., SCHLICHTING P., JUHL E., POULSEN H., TYGSTRUP N. Aspects of natural history of gastrointestinal bleeding in cirrhosis and the effect of prednisone. *Gastroenterology*, 1981, **81** : 944-952.
4. D'AMICO G., LUCA A. Natural history. Clinical-haemodynamiccorrelations. Prediction of the risk of bleeding. *Bailliere Clin. Gastroenterol.*, 1997, **11** : 243-256.
5. MERLI M., NICOLINI G., ANGELONI S., RINALDI V., DE SANTIS A., MERKEL C. *et al.* Incidence and natural history of small oesophageal varices in cirrhotic patients. *J. Hepatol.*, 2003, **38** : 266-272.
6. MERKEL C., MARIN R., ANGELI P., ZANELLA P., FELDER M., BERNARDINELLO E. *et al.* A placebo-controlled clinical trial of nadolol in the prophylaxis of growth of small oesophageal varices in cirrhosis. *Gastroenterology*, 2004, **2** : 476-484.
7. ZOLI M., MERKEL C., MAGALOTTI D., GUELI C., GRIMALDI M., GATTA A. *et al.* Natural history of cirrhotic patients with small oesophageal varices : a prospective study. *Am. J. Gastroenterol.*, 2000, **2** : 503-508.
8. DEFRANCHIS R. Evaluation and follow-up of patients with cirrhosis and oesophageal varices. *J. Hepatol.*, 2003, **38** : 361-363.
9. 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.*, 2006, **1** : 217-231.
10. GRAHAM D.Y., SMITH J.L. The course of patients after variceal hemorrhage. *Gastroenterology*, 1981, **80** : 800-809.
11. JENSEN D.M. Endoscopic screening for varices in cirrhosis : findings, implications, and outcomes. *Gastroenterology*, 2002, **122** : 1620-1630.
12. BHASIN D.K., MALHI NJ. Variceal bleeding and portal hypertension : much to learn, much to explore. *Endoscopy*, 2002, **34** : 119-128.
13. MERKEL C., ZOLI M., SIRINGO S., VAN BUUREN H., MAGALOTTI D., ANGELI P., SACERDOTI D., BOLONDI L., GATTA A. Prognostic-indicators of risk for first variceal bleeding in cirrhosis : a multicenter study in 711 patients to validate and improve the North Italian Endoscopic Club (NIEC) index. *Am. J. Gastroenterol.*, 2000, **95** : 2915-2920.
14. D'AMICO G., PAGLIARO L., BOSCH J. Pharmacologic treatment of portal hypertension : an evidence-based approach. *Semin. Liver Dis.*, 1999, **19** : 475-505.
15. IMPERIALE F.T., CHALASANI N. A meta-analysis of endoscopic variceal ligation for primary prophylaxis of oesophageal variceal bleeding. *Hepatology*, 2001, **33** : 802-807.
16. DEFRANCHIS R. Developing consensus in portal hypertension. *J. Hepatol.*, 1996, **25** : 390-394.
17. GRACE N.D., GROSZMANN R.J., GARCIA-TSAO G., BURROUGHS A.K., PAGLIARO L., MAKUCH R.W. *et al.* Portal hypertension and variceal bleeding : an AASLD single topic symposium. *Hepatology*, 1998, **28** : 868-880.
18. JALAN R., HAYES P.C. UK guidelines on the management of variceal haemorrhage in cirrhotic patients. *Gut*, 2000, **46** (Suppl III) : 1-15.
19. DEFRANCHIS R. Updating consensus in portal hypertension. *J. Hepatol.*, 2000, **33** : 846-852.
20. DEFRANCHIS R. Evolving consensus in portal hypertension. Report of the Baveno IV Consensus Workshop on methodology of diagnosis and therapy in portal hypertension. *J. Hepatol.*, 2005, **43** : 167-176.
21. GARCIA-TSAO G., SANYAL A.J., GRACE N.D., CAREY W. Prevention and management of gastrooesophagealvarices and variceal hemorrhage in cirrhosis. *Hepatology*, 2007, **46** : 922-938.
22. PUGH R.N., MURRAY-LYON I.M., DAWSON J.L., PIETRONI M.C., WILLIAMS R. Transection of the oesophagus for bleeding oesophageal varices. *Br. J. Surg.*, 1973, **60** : 646-649.
23. ALEMPIJEVIC T., BULAT V., DJURANOVIC S., KOVACEVIC N., JESIC R., TOMIC D., KRSTIC S., KRSTIC M. Right liver lobe/albumin ratio : Contribution to non-invasive assessment of portal hypertension. *World J. Gastroenterol.*, 2007, **13** : 5331-5335
24. D'AMICO G., DE FRANCHIS R. ; COOPERATIVE STUDY GROUP. Upper digestive bleeding in cirrhosis.Post-therapeutic outcome and prognostic indicators. *Hepatology*, 2003, **38** : 599-612.
25. CHALASANI N., KAHI C., FRANCOIS F. *et al.* Improved patient survival after acute variceal bleeding : A multicenter, cohort study. *Am. J. Gastroenterol.*, 2003, **98** : 653-9.
26. CARBONELL N., PAUWELS A., SERFATY L. *et al.* Improved survival after variceal bleeding in patients with cirrhosis over the past two decades. *Hepatology*, 2004, **40** : 652-9.
27. DI FIORE F., LECLEIRE S., MERLE V. *et al.* Changes in characteristics and outcome of acute upper gastrointestinal haemorrhage : A comparison of epidemiology and practices between, 1996 and, 2000 in a multicentre French study. *Eur. J. Gastroenterol. Hepatol.*, 2005, **17** : 641-7.
28. GIANNINI E., BOTTA F., BORRO P. *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*, 2003, **52** : 12005.
29. D'AMICO G., PAGLIARO L. The clinical course of portal hypertension in liver cirrhosis. *In* : ROSSI P. (ed). Diagnostic Imaging and Imaging Guided Therapy. Berlin : Springer-Verlag, 2000 : 15-24.
30. DEFRANCHIS R. Noninvasive diagnosis of esophageal varices : Is it feasible ? *Am. J. Gastroenterol.*, 2006, **101** : 2520-22.
31. THOMOPOULOS K.C., LABROPOULOU-KARATZA C., MIMIDIS K.P. *et al.* Non-invasive predictors of the presence of large oesophageal varices in patients with cirrhosis. *Dig. Liver Dis.*, 2003, **35** : 4738.
32. MADHOTRA R., MULCAHY H.E.I., WILLNER I. *et al.* Prediction of esophageal varices in patients with cirrhosis. *J. Clin. Gastroenterol.*, 2002, **34** : 4-5.
33. CHALASANI N., IMPERIALE T.F., ISMAIL A. *et al.* Predictors of large esophageal varices in patients with cirrhosis. *Am. J. Gastroenterol.*, 1999, **94** : 3285-91.
34. ZAMAN A., HAPKE R., FLORA K. *et al.* Factors predicting the presence of esophageal or gastric varices in patients with advanced liver disease. *Am. J. Gastroenterol.*, 1999, **94** : 3292-6.
35. FREEMAN J.G., DARLOW S., COLE A.T. Platelet count as a predictor for the presence of oesophageal varices in alcoholic cirrhotic patients. *Gastroenterology*, 1999, **116** : A1211 (Abst).
36. BARCIA H.X., ROBALINO G.A., MOLINA E.G. *et al.* Clinical predictors of large varices in cirrhotic patients. *Gastrointest. Endosc.*, 1998, 47 : A78 (Abst).
37. ALACORN F., BURKE C.A., LARIVE B. Esophageal varices in patients with cirrhosis : Is screening endoscopy necessary for everyone ? *Am. J. Gastroenterol.*, 1998, **93** : 1673 (Abst).
38. PECK-RADOSAVLJEVIC M. Thrombocytopenia in liver disease. *Can. J. Gastroenterol.*, 2000, **14** (Suppl D) : 60D-6D.
39. GIANNINI E., ZAMAN A., KREIL A., FLOREANI A., DULBECCO P., TESTA E. *et al.* Platelet count/spleen diameter ratio for the non invasive diagnosis of oesophageal varices. Results of a multicenter, prospective, validation study. *Am. J. Gastroenterol.*, 2006, **101** : 2511-2519.
40. GIANNINI E.G., BOTTA F., BORRO P. *et al.* Application of the platelet count/spleen diameter ratio to rule out the presence of oesophageal varices in patients with cirrhosis : A validation study based on follow-up. *Dig. Liver Dis.*, 2005, **37** : 779-85.
41. ZIMBWA T.A., BLANSHARD C., SUBRAMANIAM A. Platelet count/spleen diameter ratio as a predictor of oesophageal varices in alcoholic cirrhosis. *Gut*, 2004, **53** : 1055.
42. KORULA J. Platelet count/spleen diameter ratio predicted the presence of esophageal varices in liver cirrhosis. *ACP J. Club*, 2004, **140** : 53.