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Utility of combined use of elastography and Von Willebrand Factor Antigen/Thrombocyte Ratio in prediction of gastroduodenal mucosal portal hypertension related vascular lesions

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Abstract---Background: Liver cirrhosis is the most important cause of portal hypertension, esophageal varices (EVs) represent its major complication as they may rupture and bleed with increased mortality rate. vWF-Ag is an established and valuable marker for determining the grade of fibrosis and cirrhosis and for mortality in patients with cirrhosis. Aim of our work is to search for the utility of combined use of elastography and Von Willebrand Factor Antigen/Thrombocyte Ratio in prediction of gastroduodenal portal hypertension related vascular lesions and identify suitable cutoff values for predicting these lesions. Patients and methods: 80 cirrhotic patients, were divided into 2 main groups, Group I included 20 patients with no evidence of portal hypertension related vascular lesions as verified by endoscopic

examination (disease control group), group II, included patients with vascular lesions and was divided into 3 subgroups groups, group IIa included 20 patients with esophageal varices or gastro-esophageal varices, group IIb included 20 patients with isolated gastric varices, group IIc included 20 patients with portal hypertension related lesions other than esophageal and gastric varices. Results: vWF Ag and VITRO score were significantly higher in patients with different vascular lesions, addition of VITRO score to the established combination of transient elastography and platelet count markedly improved the predictability of vascular lesions associating portal hypertension.

Keywords--portal hypertension, Paveno criteria, platelets, transient elastography, vWF Ag, VITRO score.

Introduction

Liver cirrhosis is the most important cause of portal hypertension. There are several factors associated with pathogenesis of portal hypertension. There is increased intrahepatic vascular resistance to the portal flow due to sinusoidal capillarization as well as fibrosis-induced distortion of the vasculature. Dynamically, there is contraction of the smooth muscles of the blood vessels, hepatic stellate cells around the sinusoids, and the myofibroblasts in the fibrous septae, in response to increased vasoconstrictors, e.g endothelins, norepinephrine, angiotensin II, cysteinyl leukotrienes and decreased intrahepatic vasodilators as nitrous oxide. Splanchnic vasodilation in response to nitrous oxide, prostacyclin, bacterial translocation, and carbon monoxide is a major cause of increased portal venous flow (1,3).

Esophageal varices (EVs), a major complication of portal hypertension, may rupture and bleed with increased mortality rate. EVs are dilated tortuous submucosal veins usually in the distal esophagus. They develop when HVPg > 10 mmHg but bleed when HVPg > 12 mmHg. Endoscopy is the gold standard for the detection and diagnosis for the follow-up of EVs (4). Current practice guidelines recommended endoscopic screening for the presence of esophageal varices in all patients with cirrhosis. If varices are not present, screening endoscopy should be repeated 2-3 years or sooner if there is evidence of hepatic decompensation. Other methods for detection of varices are ultrasonogram with Doppler study, CT scan, Gadolinium-enhanced MRI and endosonograph (5,6). Over the last decade, it has become the common practice to screen known cirrhotic patients with endoscopy to look for esophageal varices, however endoscopy is countered some times by many obstacles as patient refusal or patient unfitness, so non invasive methods for assessment of vascular lesions become essential. Several studies have recently attempted to identify non-invasive predictors of esophageal varices. They are platelet count, AST-to-ALT ratio, AST-to-platelet ratio index (APRI), Platelet count/spleen diameter ratio, Lok index, Forns' index, Fib-4 and fibroindex (7). Of these Transient elastography (TE), APRI, and Platelet count/spleen ratio are promising predictors (8). It was suggested that liver stiffness measured by shear wave elastography, a novel non-invasive technology may reflect not only fibrosis and

portal pressure but it may even predict the presence or absence of large esophageal varices, in patient with cirrhosis (9).

Von Willebrand factor antigen (VWF-Ag) is released by activated endothelial cells and is therefore an indicator of endothelial cell activation. The endothelium plays a crucial role in many vascular diseases, and endothelial dysfunction is a fundamental component of the increased hepatic vascular tone of cirrhotic livers. VWF-Ag is an established and valuable marker for determining the grade of fibrosis and cirrhosis and for mortality in patients with cirrhosis (10). Thrombocytopenia is the most common and first hematologic abnormality in patients with cirrhosis due to splenic platelet sequestration, bone marrow suppression and reduced levels or activity of the hematopoietic growth factor thrombopoietin (11). Despite wide variety of noninvasive methods for prediction of vascular bleeding with liver cirrhosis and portal hypertension, the ideal test has not yet been reached.

Patients and methods

Adult patients age ≥ 18 years who are suffering from cirrhosis irrespective of cause, child A were included in the study. Exclusion criteria, patients on treatment of portal hypertension with propranolol > 80 /day mg or carvedilol > 12.5 mg/day, patients with active variceal bleeding, decompensated cirrhosis (ascites, encephalopathy, diuretic therapy). Moreover, those who had known severe co-morbid disease, known case of hematological malignancy or bleeding disorders and morbidly obese patients were also excluded. Laboratory tests were done for all patients including liver function tests: ALT-AST-bilirubin-albumen, creatinine, CBC, platelets, tumor marker (AFP) , viral serology HCV antibody-HBsAg, assay of Von Willebrand Factor Antigen. Demographic and clinical variables as age, sex, etiology of cirrhosis of liver, jaundice, edema, testicular atrophy and gynaecomastia were also included. Endoscopy of upper GIT was done in the endoscopy department of national liver institute and endoscopic findings were classified together with related vascular lesions as esophageal and esophago-gastric, isolated gastric varices, portal hypertensive gastropathy, gastric antral vascular ectasia (watermelon stomach), portal duodenopathy and-rare vascular lesions. Liver stiffness status was performed via transient elastography, all readings were taken from right lobe of liver with patients lying at supine position. Platelet markers, platelet count, APRI test, Von Willebrand Factor Antigen and Von Willebrand Factor Antigen/Thrombocyte Ratio (VITRO) were measured and calculated.

The study involved 80 patients, they were divided into 2 main groups, Group I included 20 patients with no evidence of portal hypertension related vascular lesions as verified by endoscopic examination (disease control group), group II, included patients with vascular lesions and was divided into 3 subgroups groups, group IIa included 20 patients with esophageal varices or gastro-esophageal varices, group IIb included 20 patients with isolated gastric varices, group IIc included 20 patients with portal hypertension related lesions other than esophageal and gastric varices including portal hypertensive gastropathy, portal hypertensive duodenopathy and other vascular lesions.

Statistical analysis

Data were analyzed using the Statistical Package of Social Science (SPSS) program for Windows (Standard version 26). The normality of data was first tested with one-sample Kolmogorov-Smirnov test. Qualitative data were described using number and percent. Association between categorical variables was tested using Chi-square test. Continuous variables were presented as mean $\pm$ SD (standard deviation) for normally distributed data. The two groups were compared with independent t test while more than two groups were compared by ANOVA test. Pearson correlation was used to correlate continuous data. Sensitivity and specificity at different cutoff points were tested by ROC curve. For all above mentioned statistical tests done, the threshold of significance is fixed at 5% level (p-value). The results were considered significant when the $p \leq 0.05$. The smaller the p-value obtained, the more significant are the results.

Results

Demographic characteristics of the studied patients and etiology of the disease

Data in table 1 show that no statistically significant difference between the studied groups regarding age. Male patients represented the majority of patients and were 67 (83.7) patients, with regard to the etiology of cirrhosis 76 patients belonged to hepatitis c and only 4 patients belonged to hepatitis B virus infection.

Table 1
Demographic data and etiology among the studied groups

	Group (I) No=20	Group (IIa) No=20	Group (IIb) No=20	Group (IIc) No=20	P value
Age (Years)					
Mean $\pm$ SD	49.81 $\pm$ 11.02	53.35 $\pm$ 7.42	55.35 $\pm$ 9.52	51.15 $\pm$ 8.22	0.237
Min-Max	15-66	33-66	39-71	33-70	
Sex					
Male	18 (90.0%)	16 (80.0%)	17 (85.0%)	16 (80.0%)	0.940
Female	2 (10.0%)	4 (20.0%)	3 (15.0%)	4 (20.0%)	
Etiology					
Hepatitis B	1 (5.0%)	0 (0%)	2 (10.0%)	1 (5.0%)	0.741
Hepatitis C	19 (95.0%)	20 (100%)	18 (90.0%)	19 (95.0%)	

Group (I): Control, Group (IIa): patients with esophageal or gastro- esophageal varices, Group (IIb): patients with isolated gastric varices, Group (IIc): portal HTN with other lesions.

Data regarding laboratory investigations among the studied groups

Table 2 show that creatinine level shas no significant difference among different groups, total bilirubin was significantly higher ($P < 0.05$) only in group IIC compared to the control groups, albumen was significantly lower ($P < 0.05$) in group IIB and group IIC compared to the control group. Moreover, SGOT and SGPT were significantly higher ($P < 0.05$) in groups IIa, IIB, IIC compared to the

control group, AFP was significantly higher ($P<0.05$) in group IIc compared to the control group.

Table 2
Laboratory investigations among the studied groups

	Group (I) No=20	Group (IIa) No=20	Group (IIb) No=20	Group (IIc) No=20	Test of significance		
					P1	P2	P3
Creatinine mg/dL	1.05±0.12	1.04±0.11	1.06±.12	1.09±0.22	0.747	0.750	0.509
Total bilirubin mg/dL	1.09±0.16	1.17±0.17	1.24±0.29	1.94±0.39	0.138	0.060	≤0.001*
Albumen mg/dL	3.56±0.36	3.42±0.28	3.07±0.32	3.03±0.27	0.187	≤0.001*	≤0.001*
AFP ng/mL	5.52±2.65	5.10±2.73	8.50±2.41	7.70±3.70	0.617	0.01	0.036*
S GPT u/l	28.61± 10.73	42.75± 6.67	54.25± 10.791	60.55± 8.74	≤0.001*	≤0.001*	≤0.001*
S GOT u/l	24.09± 6.52	39.45± 7.61	35.35± 8.92	39.10± 13.77	≤0.001*	≤0.001*	≤0.001*

P1: Compares GP (I) & GP (IIa), P2: Compares GP (I) & GP (IIb), P3: Compares GP (I) & GP (IIc)

Values of Platelets, VITRO score, vWF Ag and transient elastography in patients without vascular lesions and patients with vascular lesions (table 3)

Platelets were significantly lower ($P<0.05$) in patients with vascular lesions compared to patients without vascular lesion (table 3), however VITRO score, vWF Ag and transient elastography were significantly higher ($P<0.05$) in patients with vascular lesions (groups IIa, IIb, IIc) compared to patients without vascular lesions (group I).

Table 3
Platelets, VITRO score, vWF Ag and transient elastography (TE) in patients without vascular lesions and those with vascular lesions

	Group (I) No=20	Group II (IIa, IIb, IIc) No=60	P value
vWF Ag (µg/ml)	198.61±46.30	295.70±54.25	≤0.001*
Platelets (109/L)	120.33± 30.64	108.22±17.31	0.029*
VITRO score	1.69±0.59	2.79±0.85	≤0.001*
TE kPa	12.95±4.96	30.31±12.23	≤0.001*

Different noninvasive methods for prediction of vascular lesions related to portal hypertension

ROC (Receiver operating characteristics curve) for prediction of portal hypertension related vascular lesions in groups IIa ,IIb, IIc (table 4, figure 1) show that AUC for platelets is 0.684 with Confidence interval equals 0.527-0.840 and cutoff value equals 128.00, sensitivity and specificity equals 85%, 52.4% respectively, positive predictive value (PPV) equals 83.6 and negative predictive value equals 55. AUC for vWF Ag is 0.918 with Confidence interval equals 0.856-0.980 and cutoff value equals 218.50 (µg/ml), sensitivity and specificity equals 90.7%, 66.7% respectively, positive predictive value (PPV) equals 88.7 and

negative predictive value equals 83.7. AUC for VITRO score is 0.888 with Confidence interval equals 0.789-0.988 and cutoff value equals 1.65, sensitivity and specificity equals 91.6%, 71.4% respectively, positive predictive value (PPV) equals 90.6 and negative predictive value equals 78.2.

AUC for transient elastography is 0.921 with Confidence interval equals 0.862-0.980 and cutoff value equals 19.30 kPa, sensitivity and specificity equals 91.7%, 81.4% respectively, positive predictive value (PPV) equals 90.2 and negative predictive value equals 75%. AUC for platelets and transient elastography is 0.96 with Confidence interval equals 0.91-0.98, sensitivity and specificity equals 95%, 81% respectively, positive predictive value (PPV) equals 93.7 and negative predictive value equals 80.3. AUC for VITRO score and transient elastography is 0.94 kPa with Confidence interval equals 0.90-0.97, sensitivity and specificity equals 93%, 71% respectively, positive predictive value (PPV) equals 91.7 and negative predictive value equals 80. Finally, AUC for platelets and transient elastography and VITRO score is 0.974 with Confidence interval equals 0.92-0.995, sensitivity and specificity equals 95.6%, 83% respectively, positive predictive value (PPV) equals 91.7 and negative predictive value equals 82.3%.

Table 4
Receiver operating characteristics curve (ROC) for prediction of varices groups (IIa, IIb, IIc) by Platelets, VITRO score, vWF Ag and TE

	AUC	95% CI	Cutoff	Sensitivity	Specificity	PPV	NPV
Platelets (109/L)	0.684	0.527-0.840	128.00	85%	52.4%	83.6	55
vWF Ag (µg/ml)	0.918	0.856-0.980	218.50	90.7%	66.7%	88.7	83.7
VITRO score	0.888	0.789-0.988	1.65	91.6%	71.4%	90.6	78.2
TE kPa	0.921	0.862-0.980	19.30	91.7%	81.4%	90.2	75%
Platelets + TE kPa	0.96	0.91-0.98	-	95%	81%	93.7	80.3
VITRO score + TE kPa	0.94	0.90-0.97	-	93%	71%	91.7	80
Platelets + TE kPa + VITRO score	0.974	0.92-0.995	-	95.6%	83%	91.7	82.3

AUC: Area under the curve, CI: Confidence interval, PPV: positive predictive value, NPV: negative predictive value.

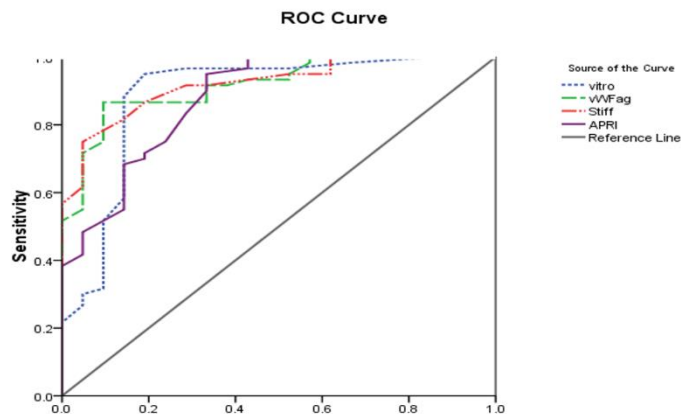


Figure 1. ROC for prediction of groups IIa, IIb & IIc by vitro, vWF Ag and TE

Discussion

Many studies along the past few decades have been introduced in attempt to early predict vascular complications of portal hypertension using noninvasive markers as platelet count, AST-to-ALT ratio, AST-to-platelet ratio index (APRI), Platelet count/ spleen diameter ratio, Lok index, Forns' index, Fib-4, fibroindex and transient elastography either individually or in a combined manner. Of these transient elastography and platelets have been studied and documented in Paveno VI and Paveno VII criteria for noninvasive prediction of vascular complications of portal hypertension, however few studies showed promising results for vWF Ag and VITRO score. In our work we aimed to clarify the possible beneficial predictive effects of these 2 new predictors and the possible additive beneficial effect for prediction of portal hypertension either when considered individually or combined together (8,7).

Regarding our work on vWF Ag we found that its serums levels were significantly higher ($P < 0.05$) in groups II ($295.70 \pm 54.25 (\mu\text{g/ml})$) when compared to the control group I ($198.61 \pm 46.30 (\mu\text{g/ml})$) (table 3). The elevated levels of vWF in cirrhosis might be a consequence of activated endothelial cells responsible for the interaction between the subendothelium at sites of vascular injury and platelets or endothelial instability resulting from increased shear stress, bacterial infection (11) or even the induced expression of vWF in the cirrhotic liver itself. Another explanation is the reduced clearance of vWF results from the decreased expression or activity of ADAMTS13 gene (vWF-Ag cleaving protease) (12).

Similarly, Lisman et al found that vWF: Ag levels were strongly elevated in plasma from patients with Child A ($165 (\mu\text{g/ml})$ - $980 (\mu\text{g/ml})$), Child B ($130 (\mu\text{g/ml})$ - $1455 (\mu\text{g/ml})$), and Child C ($385 (\mu\text{g/ml})$ - $1855 (\mu\text{g/ml})$) cirrhosis compared with the reference group in which the median vWF:Ag level was 38 - $180 (\mu\text{g/ml})$ ($p < 0.01$ for mild, moderate, and severe cirrhosis compared with control) (13). Also, Ferlitsch et al stated that vWF Ag levels were increasing with Child Pugh stage: In patients with Child A, B, and C. Median vWF Ag levels were significantly lower in the 189 compensated, compared to 97 decompensated patients ($p < 0.001$). They reported

that vWF Ag values were higher in patients with esophageal varices ($p < 0.001$) and history of ascites ($p < 0.001$), compared to patients without (14).

AUC for vWF Ag is 0.918 with Confidence interval equals 0.856-0.980 and cutoff value equals 218.50 ($\mu\text{g/ml}$), sensitivity and specificity equals 90.7%, 66.7% respectively, positive predictive value (PPV) equals 88.7 and negative predictive value equals 83.7. These results support the fact that vWF Ag is valuable in predicting different forms of vascular lesions related to portal hypertension. These results are relevant with Naglaa et al work who reported similar results with a cutoff value of 173.8 $\mu\text{g/ml}$; the sensitivity for detection of esophageal varices was 80.8%, specificity 76.0%, positive predictive value (PPV) was 93.9%, negative predictive value (NPV) was 55.6% (15). In addition, Maieron et al., concluded that vWF offers an easy possibility to evaluate the stage of fibrosis to diagnose subclinical cirrhosis in patients with chronic hepatitis C (16).

With regard to our work on VITRO score (vWF Ag to platelet ratio) we found that its serum levels were significantly higher ($P < 0.05$) in groups II (2.79 ± 0.85) when compared to the control group I (1.69 ± 0.59) (table 3). Also ROC curve for studying the possible predictive value of VITRO score in patients with portal hypertension related vascular lesions show that AUC for VITRO score is 0.888 with Confidence interval equals 0.789-0.988 and cutoff value equals 1.65, sensitivity and specificity equals 91.6%, 71.4% respectively, positive predictive value (PPV) equals 90.6 and negative predictive value equals 78.2. These results are supported by Schwarzer et al. who introduced the use of the VITRO score as a novel surrogate marker to assess the risk of decompensation and mortality in conjunction with CSPH in patients with compensated cirrhosis (17). They demonstrated that cirrhotic patients with a VITRO score > 2.5 at baseline showed a three-times higher incidence of progression to a decompensated state at the 45-month follow-up (18).

Our results showed that values of sensitivity, PPV and NPV are comparable between transient elastography and vitro with superiority for elastography regarding specificity and AUC. Taking in consideration the higher cost of elastography, VITRO appears to be a potential economic alternative. Analyzing the results of platelets + TE and comparing them with the results of VITRO score and TE we found a slight superiority for the former regarding AUC, sensitivity and specificity with no significant difference regarding PPV and NPV. An interesting finding is that when we add VITRO score to the classic combination of platelets and transient elastography there is marked superiority regarding AUC, sensitivity and specificity for the new combination, a finding that informs that noninvasive methods for prediction of vascular complications of portal hypertension still progressing towards more accuracy and more efficiency.

Conclusion

Our results that vWF Ag and VITRO score have beneficial effects in predicting vascular complications of portal hypertension and we found also that addition of VITRO score for the established combination of platelets and elastography offered a marked improvement in all parameters predicting vascular complications of portal hypertension.

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