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Von Willibrand Factor Antigen as a Non Invasive Predictor of Portal Hypertension in Patients with Liver Cirrhosis

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ABSTRACT
In cirrhotic livers, increased resistance to portal blood flow is the primary factor in the pathophysiology of portal hypertension (PH) and is caused by structural abnormalities in the hepatic vascular architecture and an increased hepatic vascular tone. Von Willebrand factor antigen (vWF Ag) is released by activated endothelial cells (ECs) and therefore represents an indicator of EC activation and plays a crucial role in high shear stress, depending on primary hemostasis. The aim of this work was to evaluate the diagnostic performance of vWF-Ag to detect clinically significant PH suggested by portal vein velocity (PVV) in patients with liver cirrhosis and to evaluate vWF-Ag levels in the prediction of decompensation.
Patients and methods: *vWF Ag was measured in thirty patients with liver cirrhosis and twenty healthy control subjects and results were correlated with portal hypertension as suggested by portal vein velocity.*
Results: *Levels of vWF Ag were significantly higher in patients with cirrhosis than healthy control subjects while levels of PVV were significantly lower. vWF Ag significantly increase in presence of ascites and shrunken liver. Levels of vWF show significant correlation with PVV and the best diagnostic cutoff value for portal hypertension was found to be 270 U/dL.*
Conclusion: *Our study shows an impressive correlation between portal hypertension and vWF levels thus can be used as noninvasive predictor of clinically significant portal hypertension (CSPH) in patients with liver cirrhosis.*
Keywords: *von Willebrand factor, portal hypertension, non invasive, cirrhosis.*

Introduction

Chronic liver diseases are characterized by progressive destruction and regeneration of the liver parenchyma leading to fibrosis and cirrhosis. Clinically it is defined as any hepatitis lasting for 6 months or longer [1]. Cirrhosis is most commonly caused by hepatitis C and B, fatty liver disease and alcoholism, but has many other possible causes [2]. Whatever the etiology, the fibrogenic processes within the liver share similar features including the presence of an inflammatory state due to infiltrating leukocytes and macrophages and activation of ECM-producing cells and leads to progressive scarring and liver cirrhosis [3]. This scarring is major determinant of the development of portal hypertension and organ dysfunction, and may progress to primary liver cancer [4].

Portal hypertension is a serious consequence of cirrhosis that may result in life-threatening complications with increased morbidity and mortality [5]. Endothelial dysfunction is an early key event in many vascular diseases and is considered a major determinant of the increased hepatic vascular tone of cirrhotic livers [7].

Portal hypertension (PH) accounts for the major complications of liver cirrhosis, such as ascites, variceal hemorrhage and decompensation. Early diagnosis of PH is essential for the management of patients with cirrhosis. In previous studies, it has been shown that early diagnosis, leading to adequate treatment, can significantly reduce the mortality rate of PH-related complication [8].

Hepatic decompensation is the most important predictor of prognosis and mortality in patients with liver cirrhosis, with several precipitating factors contributing to the first event of decompensation [9].

Normally, portal blood flows towards the liver (hepatopetal flow). In normal patients the mean PV flow rate is 13 to 23 cm/sec but in patients with portal hypertension it tends to decrease, the mean portal vein velocity (PVV) may vary depending on the presence and location of spontaneous shunts [10].

Recent guidelines recommend the diagnosis of PH by the measurement of hepatic venous pressure gradient (HVPG). Clinically significant portal hypertension (CSPH; HVPG 10 mmHg) is associated with a higher risk of liver-related mortality, development of varices, and other PH-related complications [11]. Measurement of HVPG is an invasive procedure and is only available in specialized centers. Noninvasive markers could be a clear advantage for the management of patients with cirrhosis, but none of the markers investigated, so far, have shown satisfactory specificity and sensitivity to enter clinical routine [12].

More recently, transient elastography (TE) was described as a noninvasive tool for the diagnosis of PH in patients with liver cirrhosis, but the costs and availability of TE represent limiting factors in smaller hospitals. Thus, the recent Baveno V consensus conference on PH recommended to investigate and identify further noninvasive markers for PH [11].

Von Willebrand factor (vWF), P-selectin and isoprostranes have been used as markers of endothelial function. In patients with angina pectoris or acute myocardial infarction, vWF levels are independent predictors of subsequent acute myocardial infarction and mortality, respectively [13]. Levels of vWF are increased in patients with cirrhosis and correlate with the severity of liver disease, with the levels of endotoxaemia and of nitric oxide [6].

Von Willebrand factor antigen (v WF-Ag) is released by activated endothelial cells (ECs) and therefore represents an indicator of EC activation and plays a crucial role in high shear stress, depending on primary hemostasis. Furthermore, in patients with liver cirrhosis, elevated levels of vWF-Ag are frequently observed [14].

vWF is a large multimeric glycoprotein present in blood plasma and produced by the endothelium (in the Weibel-Palade bodies), megakaryocytes (α-granules of platelets), and subendothelial connective tissue [15].

Although it is established that VWF-Ag is increased in patients with cirrhosis, no data on the association of vWF-Ag and portal pressure exist [6].

vWF plays an important role in primary hemostasis at sites of vascular trauma or injury, platelet subendothelial adhesion by acting as a bridge between platelet receptors and subendothelial structures [16].

The aim of this work was to evaluate the diagnostic performance of vWF Ag to detect clinically significant PH suggested by portal vein velocity in patients with liver cirrhosis and to evaluate vWF Ag levels in the prediction of decompensation.

Materials and Methods

This study was conducted on 50 subjects; 30 patients with liver cirrhosis and 20 age- and sex- matched apparently healthy subjects as a control group, in the period from November 2015 to April 2016 at Ain Shams University Hospitals. The thirty patients included in the study had ages ranging from 27 years to 66 years with median 50.5 years they were 16 (53.3%) males and 14 (46.7%) females, with a male to female ratio 8: 7. The twenty apparently healthy people included in the study had ages ranging from 24 years to 69 years with median of 49 years. They were 11 (55%) males and 9 (45%) females with a male to female ratio 11: 9.

Exclusion Criteria

Patients with gastrointestinal bleeding; infection or hepatorenal syndrome within 1 month; prothrombin rate less than 40% and bilirubin greater than 5 mg/dL; pregnancy; portal vein thrombosis; cardiac, renal or respiratory failure; previous surgical or transjugular intrahepatic portosystemic shunt; hepatocellular carcinoma; cholestatic liver disease and treatment with vasoactive drugs (including b-blockers), statins, aspirin or other non steroidal anti-inflammatory drugs,

antibiotics and antioxidants in the previous 2 weeks were excluded. The study protocol was approved by Ain Shams medical research ethical committee.

Initial Assessment

Liver cirrhosis was diagnosed clinically, biochemically or by typical radiological findings. All patients were subjected to full detailed history and careful clinical examination laying stress on etiology of liver disease, age, medical history, including the presence of bleeding esophageal varices, ascites, hepatic encephalopathy, hematological status and clinical chemistry.

Radiological Assessment

Portal vein velocity assessment using ultrasound technique by the superficial transducer after imaging of the echo pattern of the liver texture for evaluation of the cirrhotic pattern using the deep transducer by Siemens ultrasound machine of German manufacture.

Sampling

1-Two mL of venous blood samples were collected, under complete aseptic precautions, samples were dispensed into a tube containing citrate as an anticoagulant at a concentration of 0.11 mL (1 part sodium citrate solution with 9 parts venous blood). The sample was mixed well with care to avoid the formation of foam. Plasma was collected by centrifugation at 1500 rpm for not less than 15 minutes at room temperature (15 to 25 °C) for vWF Ag measurement and prothrombin concentration.

2- Two mL of venous clotted blood were withdrawn by sterile venipuncture in a tube for chemistry (SGOT, SGPT, albumin, bilirubin) on synchron CX7 autoanalyzer, Beckman Instruments, Brea, California, USA).

Methods

To each sample vWF Ag is measured using Sysmex 1500 coagulation analyzer for the quantitative determination of vWF Ag in human plasma by immunoturbidimetry, Calibration with standard human plasma was done. The standard dilutions are automatically prepared by the Sysmex coagulation analyzers by dilution with Dade Owren's Veronal buffer. The vWF Ag assay was automatically carried out by the Sysmex coagulation analyzers and the results were shown on the screen.

Statistical Methods

IBM SPSS statistics (V. 22.0, IBM Corp., USA, 2013) was used for data analysis. Data were expressed as Median and Percentiles for quantitative non-parametric measures and both number and percentage for categorized data. Comparison between two independent mean groups for parametric data was done using Student t test.

Wilcoxon Rank Sum test was done to compare between two independent groups for non-parametric data.

Ranked Spearman correlation test was done to study the possible association between each two variables among each group for non-parametric data. Chi-square test was done to study the association between each 2 variables or comparison between 2 independent groups as regards the categorized data. Receiver operating characteristic curve (ROC) analysis was employed for the determination of the performance characteristics of vWF Ag measurement. Probability or p value of <0.05 was considered statistically significant in all analyses.

Results

Clinical, laboratory and radiological characteristics of patients, and healthy controls: (table 1)

The studied patients had highly significant ($p<0.001$) higher vWF Ag levels (median; 267 U/dL, IQR; 200.75 U/dL to 293.25 U/dL) than the control group (median; 26.5 U/dL, IQR; 15.75 U/dL to 40 U/dL) as well as lower portal vein velocity (patient; median; 10.5 cm/sec, IQR; 7 cm/sec to 15 cm/sec, control; median; 20 cm/sec, IQR; 17 cm/sec to 23 cm/sec).

Table (1): Clinical, laboratory and radiological characteristics of patients, and healthy controls

Parameters	Patients (n=30)	Healthy control (n=20)	p
Age (year), median (range)	50.5 (27-66)	49 (24-69)	0.466
Males, n (%)	16 (53.5)	11 (55)	0.908
Ascites, n (%)	18 (60)	-	-
Oesophageal varices, n (%)	17 (56)	-	-
Shrunken liver, n (%)	10 (30)	-	-
Child Pugh Class, n A/B/C	12/18/0	-	-
Albumin g/dL, median(range)	3 (2.2-3.5)	-	-
SGOT, IU/L, median (range)	67.5 (11-90)	-	-
SGPT IU/L, median (range)	81 (16-103)	-	-
Prothrombin concentration %	60.3 (45.2-76.8)	-	-
PVV,cm/sec, median (range)	10.5 (7-15)	20 (17-23)	0.035
vWF, U/dL, median (range)	267 (110-330)	26.5 (10-50)	<0.001

Relation between levels of vWF Ag, PVV and signs of PH: (table 2)

vWF Ag levels were significantly ($p<0.05$) higher in patients with ascites than in patients without while PVV levels showed no significant difference between the two groups. Patients with ascites also had highly significant ($p<0.001$) higher SGOT, SGPT levels and lower albumin level.

Patients with bleeding oesophageal varices had significantly lower levels of PVV than the group without, but levels of vWF Ag showed no significant difference between the two groups.

A significant higher level of vWF Ag was found in patients with shrunken liver than patients with normal liver size while there was no significant difference as regards PVV.

Relation between levels of vWF-Ag, PVV and Child Pugh Class:

Levels of vWF Ag were significantly higher ($p<0.05$) in Child class B patients (median; 283.5 U/dL, IQR; 216 U/dL to 300 U/dL) than class A patients (median; 215.5 U/dL, IQR; 192.5 U/dL to 275 U/dL) whereas no significant difference was found in PVV between both classes (Class A; median; 11 cm/sec, IQR; 8.5 cm/sec to 14 cm/sec, Class B; median; 10 cm/sec, IQR; 7.5 cm/sec to 13.5 cm/sec).

Table (2): Comparison between groups of patients according to presence of ascites, oesophageal varices and shrunken liver.

	ascites (n=18)	No ascites (n=12)	Varices (n=17)	No varices (n=13)	shrunken liver (n=10)	Normal liver size (n=20)	p1	p2	p3
Alb(g/dl)	2.8	3.15	2.8	3	2.75	3	0.001	0.017	0.035
SGPT (IU/L)	55	73.5	60	74	67.5	62.5	0.009	0.062	0.843
SGOT (IU/L)	70.5	85	76	84	82	76.5	0.007	0.201	0.427
PT C%	55.6	70.2	61.5	67.8	48.2	68.1	0.038	0.422	0.040
PVV (cm/sec.)	10	11	8	14	12	11	0.521	0.003	0.673
vWF (U/dL)	283.5	215.5	280	210	285	224	0.046	0.107	0.036

p1 for comparison between patients with ascites and those without, p2 for comparison between patients with bleeding oesophageal varices and those without and p3 for comparison between patients with shrunken liver and those with normal liver size.

Correlation between vWF and studied parameters: (table 3)

A highly significant correlation was found between vWF and PVV where as no significant correlation was detected as regards the rest of the parameters (age, albumin, SGPT, SGOT, prothrombin concentration).

Table (3): Correlation between vWF and studied parameters.

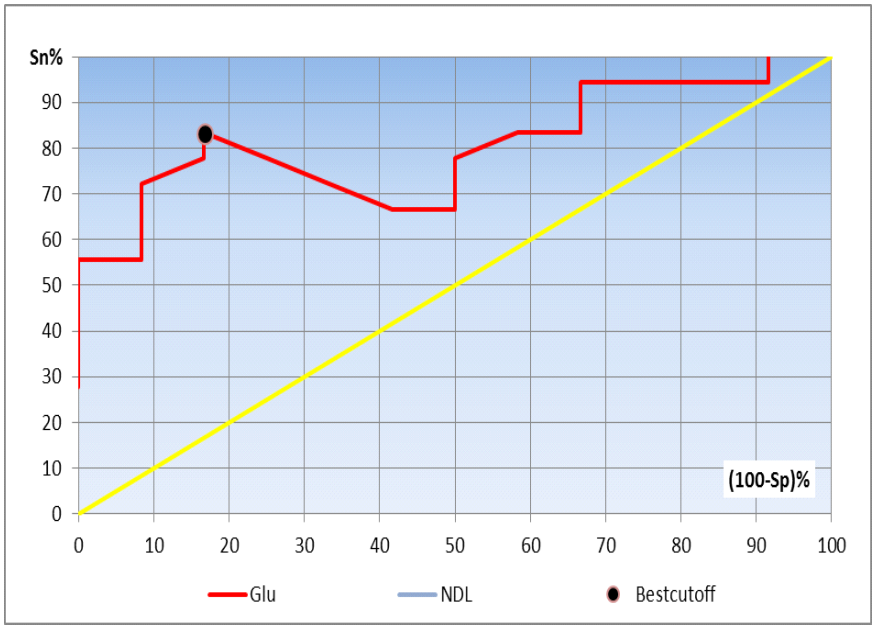
	Vwf		
	R	P	Sig.
Age(yrs)	0.058	0.762	NS
Alb (g/dl)	-0.316	0.089	NS
SGPT(IU/L)	0.125	0.51	NS
SGOT(IU/L)	0.171	0.366	NS
PT C%	-0.512	0.090	NS
PVV(cm/sec.)	-0.774	**<0.001**	HS

Determination of the best cut off level for vWF:

Roc curve analysis was performed to determine the best diagnostic cut off value to discriminate between patients with portal hypertension and those without portal hypertension according to the portal vein velocity, and it revealed that vWF level of 270 U/dl as the best cut off value with specificity 83.3 and sensitivity 83.3 (table 4) (figure 1).

Table (4): Diagnostic Validity Test: between patients with PVV <13 cm/sec & those ≥13 cm/sec.

VWF	TN	FN	FP	TP	SP	SN	P-	P+	Eff
110	1	0	11	18	8.3	100.0	100.0	62.1	63.3
118	1	1	11	17	8.3	94.4	50.0	60.7	60.0
165	2	1	10	17	16.7	94.4	66.7	63.0	63.3
190	4	1	8	17	33.3	94.4	80.0	68.0	70.0
200	4	3	8	15	33.3	83.3	57.1	65.2	63.3
201	5	3	7	15	41.7	83.3	62.5	68.2	66.7
210	6	4	6	14	50.0	77.8	60.0	70.0	66.7
218	6	5	6	13	50.0	72.2	54.5	68.4	63.3
230	6	6	6	12	50.0	66.7	50.0	66.7	60.0
251	7	6	5	12	58.3	66.7	53.8	70.6	63.3
260	8	5	4	13	66.7	72.2	61.5	76.5	70.0
264	9	4	3	14	75.0	77.8	69.2	82.4	76.7
270	**10**	**3**	**2**	**15**	**83.3**	**83.3**	**76.9**	**88.2**	**83.3**
280	10	4	2	14	83.3	77.8	71.4	87.5	80.0
281	11	5	1	13	91.7	72.2	68.8	92.9	80.0
286	11	8	1	10	91.7	55.6	57.9	90.9	70.0
290	11	8	1	10	91.7	55.6	57.9	90.9	70.0
291	12	8	0	10	100.0	55.6	60.0	100.0	73.3
300	12	8	0	10	100.0	55.6	60.0	100.0	73.3
301	12	10	0	8	100.0	44.4	54.5	100.0	66.7
310	12	13	0	5	100.0	27.8	48.0	100.0	56.7



AUC vWF: 0.858

Fig. (1): ROC curve analysis showing the diagnostic performance of vWF for discriminating patients with PVV<13cm/sec from those ≥13cm/sec.

Discussion

Endothelial dysfunction is an early key event in vascular disorders, and its presence has been associated with poor prognosis. In cirrhosis, endothelial dysfunction in the hepatic vascular bed is considered a major determinant of the increased vascular tone of cirrhotic livers and therefore of the development of portal hypertension [6].

The elevated levels of vWF Ag in cirrhosis may be a consequence of endothelial perturbation, caused by increased shear stress, bacterial infection, or induction of

the synthesis of vWF Ag in the cirrhotic liver itself. Reduced clearance of vWF Ag resulting from decreased expression or activity of ADAMTS13 (vWF Ag cleaving protease) may further increase vWF Ag levels in patients with cirrhosis with PH. Clinical consequences of cirrhosis are foremost related to CSPH more than to any other cause which prompted the proposal of a new staging system for patients with cirrhosis [12].

In our study levels of vWF Ag were highly significantly elevated and levels of PVV were significantly lower in patients with cirrhosis than age and sex matched control individuals. vWF Ag levels showed significant increase in cirrhotic patients with ascites and shrunken liver versus those without but they showed no significant difference as regards bleeding oesophageal varices. Moreover, levels of vWF Ag were significantly higher in Child class B patients than class A patients whereas no significant difference was found in PVV between both classes.

Similarly, Lisman et al [14] found that vWF: Ag levels were strongly elevated in plasma from patients with Child A (380% [165-980]; median [range]), Child B (500% [130-1455]), and Child C (760% [385-1855]) cirrhosis compared with the reference group in which the median VWF: Ag level was 107% [38-180]) ($p < 0.01$ for mild, moderate, and severe cirrhosis compared with control). But they stated that, the functional capacity of the vWF decreased with increasing severity of the disease as shown by a reduction in vWF: RCO/vWF: Ag ratio and reduced collagen binding capacity. Despite the suppressed binding capacity to both glycoprotein Ib and collagen, the highly elevated vWF levels in plasma from patients with cirrhosis resulted in a substantially elevated platelet deposition to collagen in a vWF-dependent, flow-driven platelet adhesion assay. This indicates that the quantitative increase vWF in cirrhosis overrules the qualitative defects, and that the elevated levels of vWF might in part compensate for the qualitative and quantitative platelet defects found in these patients.

Also, Ferlitsch et al [12] stated that vWF Ag levels were increasing with Child Pugh stage: In patients with Child A vWF Ag was 240% (IQR 181%-325%), in Child B 350 % (IQR 288%-435%), and in Child C 452% (IQR 353%-594%). 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. Higher vWF Ag levels were significantly associated with varices (OR = 3.27; $p < 0.001$) and ascites (OR = 3.93; $p < 0.001$).

Furthermore, La Mura et al [6] found that in patients with cirrhosis peripheral levels of vWF were significantly increased (vWF 222+/-17 U/dl vs 104+/-13 U/dl in healthy controls, $p<0.001$).

In our study, a highly significant correlation was found between vWF and PVV while there is no significant correlation was detected as regards the rest of the parameters (age, sex, albumin, SGPT, SGOT).

In accordance with our results La Mura et al [6] stated that a positive linear correlation was found between peripheral levels of vWF and HVPG ($r=0.47$, $p<0.001$)

Similarly Ferlitsch, et al.[12] stated that vWF and HVPG values correlated significantly ($r = 0.643$, $P < 0.001$). Linear regression showed an increase of HVPG values of 2.9 mmHg per increase of vWF Ag level of 100 points ($P < 0.0001$). AUC for the diagnosis of CSPH was 0.884 (CI: 0.841-0.928) and 0.88 (CI: 0.84-0.92) for the diagnosis of severe PH (HVPG 12 mmHg .The invasiveness and lack of general availability of HVPG measurement prevents the broad use of pressure-guided diagnostic and therapeutic algorithms in patients with cirrhosis. So in our study we measured PVV instead of HVPG and we found that PVV significantly decrease in cirrhotic patients with signs of portal hypertension.

Similarly Chawla, et al [17] reported significant decrease in PVV as the cirrhosis progressed.

In our study ROC curve analysis was performed to determine the best diagnostic cut off value to discriminate between patients with portal hypertension and those without portal hypertension according to the portal vein velocity, and it revealed that vWF Ag level of 270 U/dl as the best cut off value with specificity 83.3 and sensitivity 83.3.

In line with our results, Ferlitsch, et al [12] reported cut-off level 241 U/dl, which represents the optimal cutoff to discriminate between the presence or absence of CSPH in patients with cirrhosis.

In accordance with our results, La Mura et al [6] stated the existence of a potential cut-off of vWF useful to discriminate patients for the risk of developing this combined endpoint, the cohort was split according to the cut-off of 216 U/dl disclosed by the Youden index as the value of vWF that maximized the sum of sensitivity (84%) and specificity (61%).Patients with peripheral levels of vWF below this value had a significantly higher probability of survival free of portal hypertension-related complications and transplantation than patients with vWF above 216 U/dl (87% vs 22%, $p=0.001$).

In conclusion, our study shows an impressive correlation between portal pressure and vWF-Ag levels. The

measurement of vWF Ag represents a valuable, accessible, and affordable noninvasive predictor of CSPH in patients with liver cirrhosis. It has the potential to enter clinically relevant diagnostic and therapeutic algorithms for patients with cirrhosis. Further prospective studies on the prognostic value of vWF Ag levels are warranted to assess their role in the potential risk stratification of patients with cirrhosis with PH.

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