Global Advanced Research Journal of Medicine and Medical Sciences (ISSN: 2315-5159) Vol. 6(11) pp. 302-309, November, 2017
Available online http://garj.org/garjmms

Full Length Research Paper

Significance of von Willebrand Factor in Compensated and Decompensated Cirrhosis

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Accepted 22 November, 2017

Liver cirrhosis is associated with extensive alternations in hemostatic functions. Among these alternations, von Willebrand factor (vWF) is found to be elevated. However, its clinical significance is not well established. To demonstrate the relation between vWF level and platelet function and its relation to portal hypertension in patients with liver cirrhosis of different severity. 70 patients with liver cirrhosis were compared to 20 healthy control subjects. For all participants; vWF antigen (Ag) was measured by enzyme-linked immunosorbent assay. von Willebrand factor: ristocetin cofactor activity (vWF:RCo) –a measure of ability of vWF to interact with platelet glycoprotein Ib-was measured by agglutination technique. Ratio between vWF: RCo to VWF Ag which reflects the functional capacity of vWF was calculated (RCo/Ag ratio). Portal hypertension (PH) was assessed in patients group by portal vein duplex, congestion index and esophagogastroduodenoscopy (EGD). vWF Ag and vWF:RCo are significantly increased in patients group compared to control (31.6µg/ml and 94.5% compared to 9.4µg/ml and 65.3% respectively) while RCo/Ag ratio is significantly lower in patients group compared to control (4.2 and 8.6 respectively) indicating a reduction in the functional capacity of vWF. There is a significant positive correlation between vWF Ag and Child Pugh score of the patients and a strong positive correlation between vWF Ag and severity of PH. vWF level at cut off value 14.85µg/ml can predict PH with 98.1% sensitivity and 88.9% specificity. vWF Ag and vWF: RCo are increased in patients with liver cirrhosis. Their increase is positively correlated with severity of liver cirrhosis and partially compensate for reduced platelet count. vWF Ag is sensitive and non-invasive predictor of PH.

Keywords: vWF, ristocetin, liver Cirrhosis, portal hypertension.

INTRODUCTION

Patients with liver cirrhosis suffer from complex abnormalities of the hemostatic system that affect primary hemostasis, secondary hemostasis and fibrinolysis (Lisman and Leebeek, 2007). Changes occur in procoagulant and anticoagulant proteins as well as profibrinolytic and antifibrinolytic proteins. Thus, patients with chronic liver disease can clinically present with an increased bleeding risk or an increased risk of venous thrombosis (Tripodi and Mannucci, 2011).

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Among these abnormalities, Thrombocytopenia is a typical feature of chronic liver disease (Tripodi and Mannucci, 2007). The etiology of thrombocytopenia is multifactorial. It is believed to result from imbalance between platelet production and platelet survival (Potze et al., 2015). Reduced platelets count is partially compensated by the elevated level of Von willebrand factor (vWF) (Tripodi and Mannucci, 2011; Tripodi and Mannucci, 2007; Potze et al., 2015).

vWF is a large adhesive protein released by activated endothelial cells (Ruggeri, 1997).The function of vWF is to promote thrombus formation either directly, by mediating the adhesion of platelets to the injured vessel wall and to one another, and indirectly, by associating with factor VIII and preventing its rapid clearance from the plasma thus allowing normal thrombin generation (Ruggeri, 2003).

The elevated level of vWF in liver cirrhosis may be a consequence of endothelial damage which has been suggested to be stimulated by endotoxemia and portal hypertension (La Mura et al., 2011). Other possible mechanisms are induction of synthesis in the cirrhotic liver itself or reduced liver mediated clearance. Also, the vWF cleaving protease, a disintegrin and metalloprotease with thrombospondin type 1 motif 13, (ADAMTS13) is reduced in cirrhosis which elevates the level of vWF (Potze et al., 2015; Zheng, 2015).

AIM OF WORK

To study the relation between vWF and platelets function in patients with liver cirrhosis and identify the value of its measurement in patients with different severity of liver cirrhosis and portal hypertension.

SUBJECTS AND METHODS

Seventy patients (group I) with liver cirrhosis secondary to chronic hepatitis C infection were included in the study. They were classified according to Child Pugh classification into Child A, B and C. (Child Pugh A are compensated cirrhosis while Child Pugh B and C are decompensated patients) In addition, MELD score was calculated for each patient. A group of 20 healthy control subjects (group II) was used to establish reference values for measured assays. The study aim and protocol were explained to the included subjects and they were asked to provide a written consent before enrollment. The study design was approved by the scientific and ethical committee of Ain Shams University Hospitals.

Exclusion criteria

1. Subjects with associated blood disease.
2. Cirrhosis due to causes other than chronic hepatitis C infection.
3. Hepatocellular carcinoma.

Study Design

Medical history and clinical examination were recorded in separate sheet for each patient together with collected basic laboratory data including: CBC, AST, ALT, total and direct bilirubin, total protein, albumin, PT, PTT together with renal functions and AFP.

The following scores were calculated to all patients: modified Child-Pugh score (Pugh et al., 1973) and the MELD score. MELD score was calculated using the following formula:

MELD = 9.57 x $\log_e$ (s.creatinine) + 3.78 x $\log_e$ (total bilirubin) + 11.2 x $\log_e$ (INR) + 6.43 (Kamath and Kim, 2007).

Abdominal ultrasonography (US) was performed to all patients by single operator using Toshiba Famio Cube, probe convex 3.67 MH in addition to ***portal vein duplex*** to comment on: direction of portal blood flow, Portal vein velocity and to calculate congestion index. Congestion index is the ratio of portal vein cross-sectional area to the portal vein velocity. In normal subjects this ratio is 0.07 and a value above 0.1 suggests the diagnosis of portal hypertension (Al-Nakshabandi, 2006; Vizzutti et al., 2008).

> *Thus, patients group were classified according to congestion index into group with portal hypertension (congestion index ≥ 0.1) and a group without portal hypertension (congestion index < 0.1).*

Patients underwent ***esophagogastroduodenoscopy*** (EGD) using Pentax APM 3500 for evaluation of the presence, number and grade of esophageal varices (OV) and portal hypertensive gastropathy (PHG).OV and PHG were graded according to Japanese Research for Portal Hypertension Classification System as follows (Ghweil et al., 2014).

Grading of esophageal varices

- Grade 1: small OV which flatten with insufflations or minimally protrude into the esophageal lumen.
- Grade 2: moderate sized OV with minimal obscuring of the gastroesophageal junction.

- Grade 3: large varices substantially obscuring the gastroesophageal junction.
- Grade 4: very large varices completely obscuring the gastroesophageal junction and do not flatten on insuflation.

Grading of PHG

- Mild: Mosaic like pattern.
- Severe: Mosaic like pattern with superimposed red signs.

Sample collection, preparation and storage

Blood samples were withdrawn from patients and controls for CBC, liver profile, coagulation profile in addition to vWF Ag, vWF: RCo, and RCo/Ag ratio. For coagulation and vWF studies, blood samples were collected on sodium citrate and centrifuged at 3000 x g for 10 minutes. Plasma samples were stored at -20^{0}C or below for up to 3 months. Repeated freeze-thaw cycles were avoided. Samples were batch tested weekly following thawing of the plasma for 5 minutes at 37°C.

❖ **vWF:Ag Assay**

The Assay Max vWF assay kit (Assay Pro; 3400 Harry S Truman Blvd, St. Charles, United States) employs a quantitative sandwich enzyme immunoassay technique. A monoclonal antibody specific for vWF has been pre-coated onto a 96-well microplate with removable strips. Human vWF in standards and samples is sandwiched by the immobilized antibody and the biotinylated antibody specific for vWF, which is recognized by a streptavidin-peroxidase conjugate. All unbound material is then washed away and a peroxidase enzyme substrate is added. The color development is stopped and the intensity of the color is measured.

❖ **vWF:RCo Assay**

vWF:RCo Assay was performed on the SysmexCA-1500 (Milton Keynes, UK) using an automated VWF:RCo assay (BC Von Willebrand Reagent, Siemens, Marberg, Germany). Reaction cuvettes with stirrer bars (SB-cuvettes) were loaded on to the analyzer. This was achieved using a SB-cuvette loading tool, with which the 4 SB-cuvettes were taken at a time from their storage tray and inserted into the analyzer. BC von Willebrand reagent (Siemens Healthcare Diagnostics) was reconstituted using distilled water, mixed by vortexing and placed on the analyzer. An automated three-point calibration curve in quadruplicate was processed on the analyzer using standard human plasma (SHP, Siemens Healthcare Diagnostics) diluted in Owrens veronal buffer (OVB, Siemens Healthcare Diagnostics). Samples, again diluted in OVB, were subsequently tested using one of two automated multi-dilution analysis (MDA) series. MDA is the system whereby the analyzer automatically makes up to three dilutions of the tested plasma, and subsequently assesses linearity of the dose response and parallelism with calibration curve. Thus, making it possible to look for falsely low results caused by inhibitory activity or falsely high results caused by activation.

In the assay, plasma vWF binds to the platelet gp1b receptor on lyophilized reagent platelets and agglutinates the platelets in the presence of the antibiotic Ristocetin. Agglutinated platelets decrease reagent turbidity which is measured at 405 nm with reduced light transmittance proportional to plasma VWF. vWF levels are obtained using the pre-programmed standard curve and presented as vWF %. Samples with a vWF result below 50% were retested against a calibration curve established for low values.

❖ **Calculation of vWF:RCo/vWF Ag ratio**

This ratio is an indicator of the functional capacity of the vWF Ag (Lisman et al., 2006).

Statistical Methods

Data were analyzed using PASW (predictive analysis software) version 18 (IBM© Corp., Armonk, NY, USA).Normality of data was tested using D'Agostino-Pearson test, normally distributed numerical variables were presented as mean ± SD (standard deviation).Numerical data were compared using unpaired t test, qualitative data were compared using chi-square t test, or Fisher exact test. Correlations among numerical variables were tested using the Pearson product-moment correlation. Receiver-operating characteristic (ROC) curve analysis was used to examine the value of a quantitative variable for discrimination between the categories of a binary variable. A two-sided P-value (probability of chance) ≤0.05 was considered statistically significant.

Table 1. Clinical, sonographic and endoscopic criteria of patient group

Patient criteria		Count (%)
1.Clinical		
Child score	A	20 (28.6%)
	B	25 (35.7%)
	C	25 (35.7%)
Hepatic encephalopathy	No	50 (71.4%)
	Yes	20 (28.6%)
Mean MELD score±SD	15±6.1	
2.Ultrasound		
Ascites	No	20 (28.6%)
	Yes	50 (71.4%)
Portal vein patency	Thrombosed	5 (7.1%)
	Patent	65 (92.9%)
Splenic vein patency	Thrombosed	0 (0%)
	Patent	70 (100%)
3.Endoscopic		
OV grade*	Absent	18 (25.7%)
	I	13 (18.6%)
	II	12 (17.1%)
	III	13 (18.6%)
	IV	14 (20%)
PHG*	No	15 (21.4%)
	Mild	32 (45.7%)
	Severe	23 (32.9%)

***OV** oesophogeal varices ***PHG** Portal hypertensive gastropathy

Table 2. Mean values of vWF Ag, vWF:RCo and RCo/Ag ratio in both groups

Variables (values in mean±SD)	Group I	Group II	P value
vWF Ag(3-15 µg/ml)	31.6±24.5	9.4±5.1	≤ 0.01
vWF:RCo (70-150%)	94.5±32.4	65.3±31.7	≤ 0.01
RCo/Ag ratio	4.2±2.7	8.6±5.5	≤ 0.01

RESULTS

Table 1 shows the clinical, sonographic and endoscopic criteria of patients group.

We had 20 patients with compensated cirrhosis and 50 patients with decompensated cirrhosis. All decompensated patients had history of encephalopathy, as cites in abdominal ultrasound and PHG and different grades of OV on EGD (table 1).

There was a statistically significant difference between patients with liver cirrhosis (group I) and control group (group II) as regard vWF Ag, vWF:RCo and RCo/Ag ratio as shown in (table 2).

The ratio between RCo /Ag level is significantly lower in patients compared to control group indicating decreased functional capacity of vWF Ag in patients group (table 2).

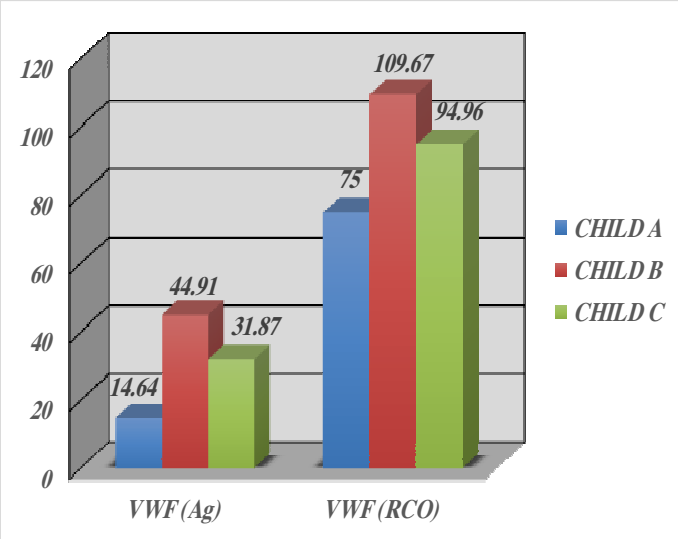

Figure 1. Comparison between vWF Ag and vWF:RCo and Child Pugh score of the patient group

I. vWF Ag, vWF:RCo, and RCo/Ag ratio in relation to severity of liver disease

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Figure 1 shows the difference between compensated (Child A) and decompensated (Child B and C) patients; a significant difference of vWF and vWF:RCo was found. Patients with decompensated cirrhosis had higher mean values compared to Child A. The ratio between RCo/Ag in compensated patients (Child A) was significantly higher (5.44±1.99) compared to decompensated patients (3.72±2.81) (table 3).

Figure (2) shows a positive significant correlation between Child score and vWF Ag.; progressive decompensation in liver condition is associated with increase in vWF Ag.

II. vWF Ag, vWF:RCo, and RCo/Ag ratio in relation to portal hypertension

Table 4 shows that patients with portal hypertension (Congestion index ≥ 0.1) had significantly different other non-invasive parameters of portal hypertension (PH) compared to non PH group; lower platelets count, higher portal vein diameter and portal vein cross section as well as size of the spleen. In such group with evidence of PH; vWF Ag and vWF:RCO were significantly higher than group without PH but the ratio between RCO to vWF was significantly less.

Comparison between patients with different grades of OV showed progressive increase in both vWF Ag and vWF:RCo with increased grade of varices as evaluated by EGD (figure 3).

The correlation between vWF Ag level and vWF:RCo was significantly positive (table 5). Thus, the increase in

Table 3. Comparison between vWF Ag, vWF:RCo and RCo/Ag ratio in compensated and decompensated patients.

	Compensated patients (n=20)	Decompensated patients (n=50)	P value
vWF Ag (3-15µg/ml) (mean±SD)	14.64±4.03	38.39±26	≤ 0.01
vWF:RCo(70-150%) (mean±SD)	75±17.94	102.31±33.74	≤ 0.01
RCo/Ag ratio (mean±SD)	5.44±1.99	3.72±2.81	≤0.05

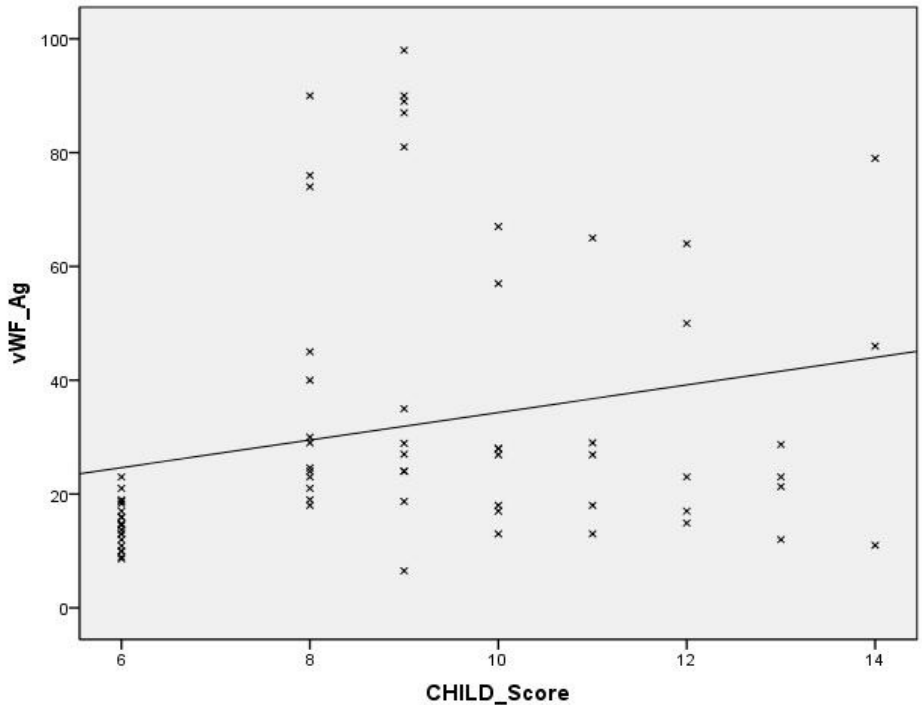

Figure 2. Scatter-plot showing significant positive correlation between vWF Ag and Child score.

Table 4. Comparison between patients with and without portal hypertension

Parameters (mean±SD)	Congestion index ≥0.1 (n.52)	Congestion index<0.1 (n.18)	P value
Plt (150000-400000/mm3)	90.62±51.11	125.33±67.03	≤0.05
MELD score	16.04±5.92	12.10±6.01	≤0.01
Child score	9.37±2.14	7.44±2.66	≤0.01
vWF Ag (3-15 µg/ml)	37.76±25.45	13.82±6.86	≤0.01
vWF:RCo (70-150%)	101.43±33.66	74.53±17.32	≤0.01
RCo/Ag ratio	3.61±2.64	5.95±2.15	≤0.01
Portal vein diameter(10-14 mm)	14.14±2.86	13.07±2.80	>0.05
Portal vein cross section (cm^2)	2.30±0.73	0.96±0.26	≤0.01
Portal vein flow velocity (13-23 cm/sec)	15.40±3.58	16.93±2.90	>0.05
Spleen size (up to 12 cm)	15.77±4.48	12.96±2.49	≤0.01
Splenic vein diameter (up to 12 mm)	14.52±2.34	12.33±2.36	≤0.01

vWF Ag is associated with increase in its ability to interact with platelet glycoprotein 1b. Increase in severity of liver disease (Child and MELD scores) or presence of more severe PH (High congestion index, more varices or less platelets count) is associated with increase in vWF Ag (table 5).

Table 6 shows that vWF Ag had the best sensitivity (98.1%) and specificity (88.9%) for prediction of portal hypertension at cut off value ≥ 14.85 µg/ml (figure 4).

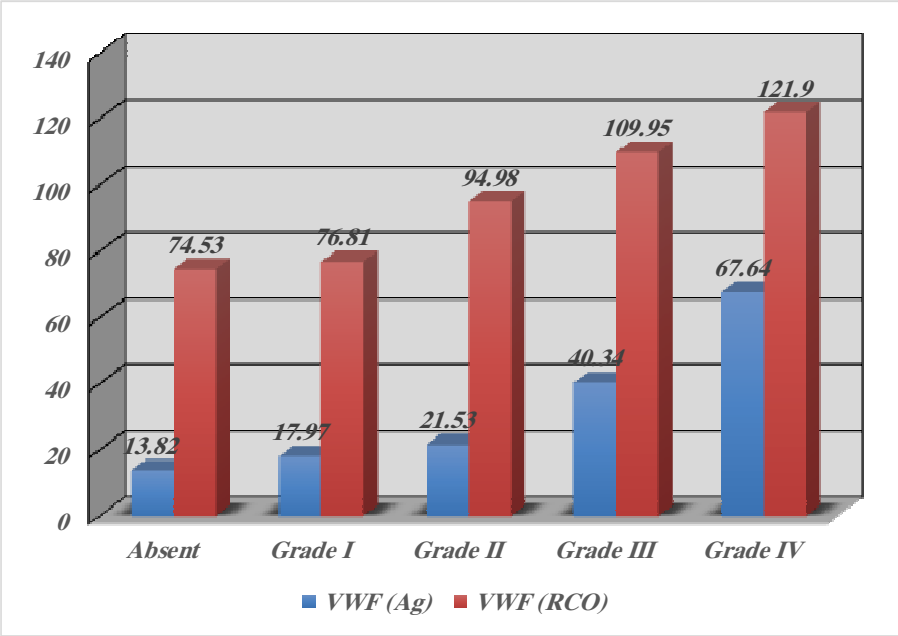

Figure 3. Comparison between vWF Ag and vWF:RCo and OV grade.

Table 5. Correlation between vWF Ag & other parameters

	vWFAg	
	r	P value
vWF:RCo	0.598	≤0.01
Child	0.239	≤0.05
MELD	0.198	>0.05
Congestion index	0.619	≤0.01
Number of OV	0.509	≤0.01
Platelet count	-0.252	≤0.05

Table 6. Diagnostic performance of non-invasive predictors of portal hypertension

	Accuracy	Cut Off	Sensitivity	Specificity	PPV	NPV
vWF Ag(3-15 µg/ml)	94.2 %	≥ 14.85	98.1 %	88.9 %	96.2 %	94.1 %
RCo/Ag ratio	83.1 %	≤ 4.77	78.8 %	77.8 %	91.1 %	56 %
Spleen size(up to 12 cm)	77.5 %	≥ 12.4	86.5 %	61.1 %	86.5 %	61.1 %
Splenic vein diameter(up to12mm)	76.3 %	≥ 12.2	84.6 %	66.7 %	88 %	6 %
vWF:RCo(70-150%)	76.2 %	≥ 77.25	80.8 %	61.1 %	85.7 %	52.4 %
Plt(150000-400000/mm^3)	71.1 %	≤ 100	78.8 %	55.6 %	83.7 %	47.6 %

PPV: positive predictive value, **NPV**: negative predictive value

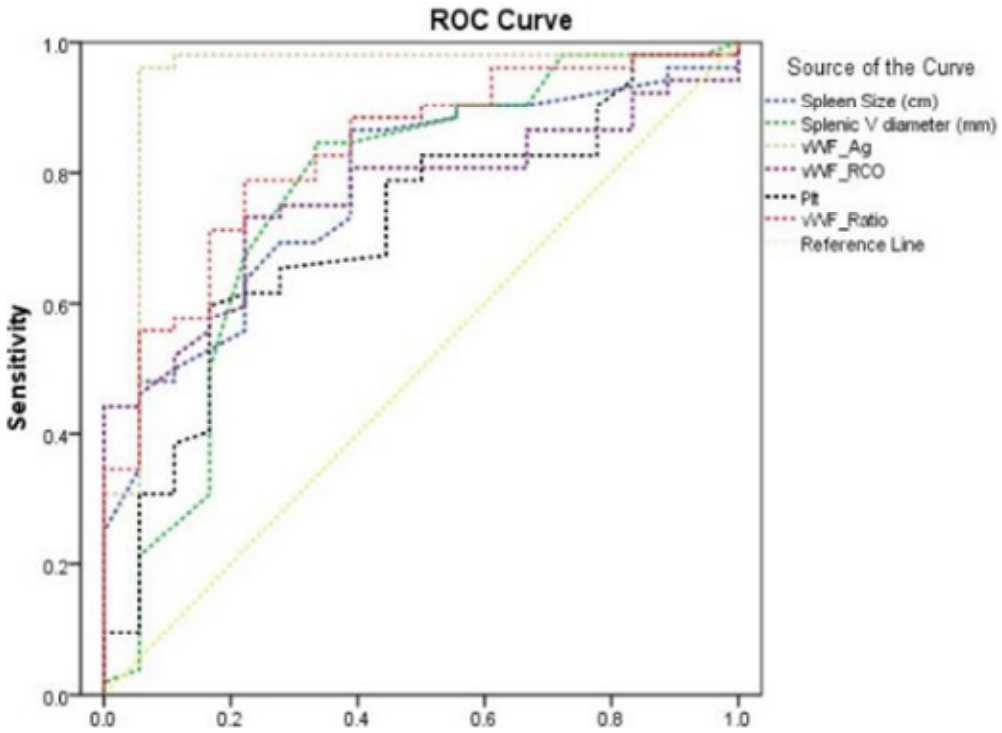

Figure 4. ROC curve for predictors of portal hypertension.

DISCUSSION

Thrombocytopenia and thrombocytopathy are often present in patients with cirrhosis. A possible compensatory mechanism for these platelets abnormality is the presence of abnormally high plasma levels of vWF (Lisman et al., 2006).

This work aimed to study the relation between vWF level and platelet function in cirrhotic patients with different severity and in the presence of portal hypertension.

I. vWF Ag and vWF:RCo in cirrhotic patients

The study showed that patients with liver cirrhosis had significantly higher serum vWF Ag levels (31.6 ± 24.5 µg/ml) compared to the normal control group (9.4 ± 5.1 µg/ml). The elevated levels of vWF in cirrhosis were suggested to reflect endothelial damage, which may be stimulated by endotoxemia associated with liver disease (La Mura et al., 2011; Lisman et al., 2006; Yilmaz et al., 2015).

We found that the increased vWF Ag was accompanied by significant increase in vWF:RCo levels in the patient group (94.5 ± 32.4%) compared to the control group (65.3 ± 31.7%) and there was a significant positive correlation between vWF Ag and vWF:RCo; higher vWF Ag was associated with increased platelet function in the form of increased ristocetin cofactor activity.

Lisman and co-workers reported a substantial elevation in vWF:RCo in patients with liver cirrhosis compared to the healthy subjects. They described RCo/Ag ratio as a measure of the functional capacity of vWF Ag in hemostasis (Lisman et al., 2006).

We measured this ratio in our work and found that it was significantly reduced in the patient group to a mean value of (4.2) compared to (8.6) in the control group.

We concluded that, although patients with liver cirrhosis had increased level of vWF Ag and associated increase in its function (vWF:RCo) to compensate for defective platelet number and function in hemostasis but still its total functional capacity is reduced (RCo/Ag ratio).

II. Relation between vWF Ag, vWF:RCo, and RCo/Ag ratio with Child Pugh score and MELD score

We compared patients with compensated liver disease (Child A) and decompensated patients(Child B and Child C); a significant higher vWF Ag level in decompensated patients was present compared to Child A patients. There was also a significant higher values of vWF:RCo in decompensated patients compared to Child A group. The presence of significant difference in such values indicated that both parameters were affected by the severity of underlying liver disease. In addition, we found a positive correlation between vWF Ag and each of Child Pugh and MELD scores.

However, RCo/Ag ratio had higher values in Child A group compared to decompensated group. A finding indicates a progressive reduction in the functional capacity of vWF Ag with progression of liver disease.

La Mura et al. and Ferlitsch et al. also reported a correlation between vWF Ag level and Child Pugh score. The association of vWF: RCo and RCo/Ag ratio with hepatocellular insufficiency was described by *Yilamz and his colleagues* (La Mura et al., 2011; Yilmaz et al., 2015; Ferlitsch et al., 2012).

III. vWF Ag, vWF:RCo, and RCo/Ag ratio and portal hypertension

We studied the relation between the measured variables (vWF Ag, vWF:RCo, and RCo/Ag ratio) and portal hypertension (PH). It was not possible to measure portal blood pressure directly in our study, so we used congestion index as an indirect measure (Al-Nakshabandi, 2006). We also measured other non-invasive parameters that reflect portal hypertension (platelet number, portal vein cross section, spleen size, and splenic vein diameter).These parameters showed a significant difference between patients with congestion index ≥ 0.1 and patients with congestion index < 0.1 indicating that congestion index is a good non- invasive alternative to the direct measurement of portal blood pressure by hepatic venous pressure gradient (HVPG).

Our measured variables (vWF Ag, vWF:RCo, and RCo/Ag ratio) were significantly different between patients with and without portal hypertension. There was a significant increase in vWF Ag and vWF:RCo and significant reduction in RCo/Ag ratio in patients with PH compared to patients without PH. Similar linear correlation between vWF Ag level and portal hypertension was reported using HVPG as a direct measure to PH (La Mura et al., 2011).

Another indicator of severity of portal hypertension used in our study was OV and its grades. Our findings showed that vWF Ag and vWF:RCo had significant higher values with higher endoscopic grading of varices. While a significant reduction in RCo/Ag ratio occurred with advance in the endoscopic grade of OV. So, we can conclude that a definite relation exists between vWF Ag and vWF:RCo and portal hypertension. vWFmay be a good non-invasive indicators of portal hypertension.

We plotted a ROC curve to find the best non-invasive predictors of portal hypertension. We found that vWF Ag level had the best sensitivity and specificity in this regard at cut off value ≥ 14.85 µg/ml which was 98.1% and 88.9% respectively.

Ferlitsch et al. reported that higher levels of vWF Ag were significantly associated with varices and that linear increase of vWF Ag elevates the risk for clinically significant portal hypertension (CSPH) and severe portal hypertension as well as associated complications (Ferlitsch et al., 2012).

REFRENCES

Al-Nakshabandi NA (2006). The role of ultrasonography in portal hypertension. The Saudi J. Gastroenterol. 12(3):111-117.

Ferlitsch M, Reiberger T, Hoke M, et al (2012). Von Willebrand Factor as new non-invasive predictor of portal hypertension, decompensation and mortality in patients with liver cirrhosis. Hepatology.

Ghweil AA, Arafa UA, Khodeary A, et al (2014). Predictors of bleeding from esophageal varices: The role of factor VII and von willebrand factor. Open J. Gastroenterol. 4:152-158.

Kamath PS, Kim WR (2007). The Model for End-Stage Liver Disease (MELD). Hepatol. 45(3): 797-805.

La Mura V, Reverter JC, Arroyo AF, et al (2011). Von Willebrand factor levels predict clinical outcome in patients with cirrhosis and portal hypertension. Gut. 60:1133-1138.

Lisman T, Bongers TN, Adelmeijer J, et al (2006). Elevated levels of von willebrand factor in cirrhosis support platelet adhesion despite reduced functional capacity. Hepatol. 44(1):53-61.

Lisman T, Leebeek FWG (2007). Hemostatic Alterations in Liver Disease: A Review on Pathophysiology, Clinical Consequences, and Treatment. Digestive Surgery. 24:250-258.

Potze W, Porte RJ, Lisman T (2015). Management of coagulation abnormalities in liver disease. Expert Rev. Gastroenetrol. Hepatopl. 9(1):103-114.

Pugh RN, Murray-Lyon IM, Dawson JL, et al (1973). Transection of the oesophagus for bleeding oesophageal varices.The Br. J. Surg. 60(8):646-649.

Ruggeri ZM (1997). Von Willebrand Factor. J. Clin. Invest. 99 (4):559-564.

Ruggeri ZM (2003). Von Willebrand factor, platelets and endothelial cell interactions. J. Thrombosis and Haemostasis. 1:1335-1342.

Tripodi A, Mannucci PM (2007). Abnormalities of hemostasis in chronic liver disease: Reappraisal of their clinical significance and need for clinical and laboratory research. J. Hepatol. 46:727-733.

Tripodi A, Mannucci PM (2011). The coagulopathy of chronic liver disease. The New England Journal of Medicine, 365:147-156.

Vizzutti F, Arena U, Rega L, et al (2008). Non invasive diagnosis of portal hypertension in cirrhotic patients. Gastroentérologie Clinique et Biologique. 32:80-87.

Yilmaz VT, Dincer D, Avci AB, et al (2015). Significant association between serum levels of Von Willebrand Factor antigen with stages of cirrhosis. The Eur. J. Med. 47:21-25.

Zheng XL (2015). ADAMTS13 and von Willebrand Factor in thrombotic thrombocytopenic purpra. The Annual Rev. Med. 66:211-225.