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Von Willebrand Factor; a New Non-Invasive Marker for Assessment of Liver Fibrosis in Infants and Children

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ABSTRACT

Background: Von Willebrand Factor (vWF) is a multimeric adhesive protein to which platelets stick. It is physiologically released by activated endothelial cells during primary hemostasis. High Shear stress induced by hyperdynamic (splanchnic) circulation in advanced hepatic fibrosis as well as endotoxinemia caused by bacterial translocation may contribute to the increased levels of vWF releasing from that activated endothelium.

Objective: The aim of the current work was to assess the stage of fibrosis changes in children with CLD noninvasively by measuring the levels of serum Vwf Ag.

Patients and Methods: This was an observational case control study conducted on sample of 40 infants and children up to 18 years divided into two equal groups of 20 cases (fibrotic) attending hepatic clinic at Mansoura University Children' Hospital and another 20 healthy matched controls. The diagnosis of fibrosis was previously verified by clinical, biochemical, ultrasonographic criteria and biopsy.

Results: There was highly statistically significant increase in vWF value in the cases compared to the controls (167.1 ± 47.8 Vs 112.9 ± 36.1 IU/dL) (P<0.001). vWF Ag values demonstrated insignificant differences concerning etiology of liver disease, presence or absence of ascites and hepatosplenomegaly (P>0.05). Values of vWF Ag were demonstrated to be significantly increases in cases with severe fibrosis as well as cases with varices (P<0.05). There were highly statistically significant correlations between vWF Ag level and both fibrosis stage and Child Score among the studied patients (P≤0.001).

Conclusion: It could be concluded Willebrand factor antigen level was positively correlated with liver function tests as well as varices and could be used as a significant predictor to severity of liver fibrosis and / or cirrhosis in children and infants with chronic liver disease.

Keywords: Von Willebrand Factor, Liver fibrosis, Infants and Children.

INTRODUCTION

Liver fibrosis is the formation of scar tissue in response to parenchymal injury secondary to chronic liver disease, e.g. chronic infection and inflammation. It distorts the normal liver parenchyma **(1).** The continuous and progressive replacement of hepatocytes by extracellular matrix and fibrous tissue leads to liver cirrhosis **(2).**

Cirrhosis is a diffuse pathophysiological state of the liver considered to be the final stage of hepatic fibrosis, characterized by chronic necroinflammatory and fibrogenetic processes, with subsequent conversion of normal liver architecture into structurally abnormal nodules, dense fibrotic septa, concomitant parenchymal exhaustion and collapse of the liver tissue **(3).**

Complications of fibrosis include jaundice, ascites, portal hypertension, gastrointestinal variceal bleeding, and hepatic encephalopathy, whose presence is indicative of decompensated disease **(4).**

Portal hypertension is a serious consequence of cirrhosis that may result in life-threatening complications with increased morbidity and mortality **(5).** Portal hypertension often results in endothelial dysfunction owing to the increased intrahepatic pressure, accompanied by changes in the hemostatic system including decrease in platelet levels and activity **(6).** The endothelium plays a crucial role in many vascular diseases and endothelial dysfunction is a fundamental component of the increased hepatic vascular tone of fibrotic livers **(7).**

Von Willebrand factor (vWF), released from activated endothelium in very high molecular weight forms, is an adhesive protein to which platelets stick. Thus, it represents an indicator of endothelial cell activation and plays a crucial role in high shear stress depending on primary hemostasis **(8).**

Currently, liver biopsy is considered as the gold standard method for stratification of hepatic fibrosis. However, liver biopsy is an invasive procedure and has limitations of sampling error and variability of histologic interpretation. Further, it is not feasible in a routine clinical setting to monitor liver fibrosis with repeated liver biopsy **(9).**

Recently, many studies conducted on adults have reported the role of elevated vWF-Ag level as a prognostic marker in chronic liver disease and it might be a key player in establishing liver fibrosis and cirrhosis **(10).**

Additionally, Other studies have reported increase of vWF-Ag level with higher Child–Pugh Score (CPS) which is considered the most widely used assessment tool for liver function and has been incorporated into algorithms for the management of patients with chronic liver disease **(11)**.

The aim of work was to investigate whether von Willebrand factor antigen level is related to severity of

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liver fibrosis and / or cirrhosis in children and infants with chronic liver disease.

PATIENTS AND METHODS

This was an observational case control study conducted on sample of 40 infants and children up to 18 years divided into two equal groups of 20 cases (fibrotic) attending hepatic clinic at Mansoura University Children' Hospital and another 20 healthy matched controls.

The diagnosis of fibrosis was previously verified by clinical, biochemical, ultrasonographic criteria and biopsy.

The fibrosis stages range from F0 to F4 according to **METAVIR system** [12] using histologic examination criteria in liver biopsy for each case: F0: no fibrosis. F1: portal fibrosis without septa. F2: portal fibrosis with few septa. F3: numerous septa without cirrhosis. F4: cirrhosis.

The group of cases in this study was classified into: Mild: F1. Moderate: F2 – F3, and severe: F4 (cirrhosis).

Inclusion criteria: Presence of fibrosis that was diagnosed on the basis of clinical, radiological, laboratory parameters and liver biopsy, and have written informed assent.

Exclusion criteria: Presence of malignancy that significantly affects survival, presence of pre and post hepatic causes of PH, presence of sever systemic illness (severe cardiopulmonary or renal impairment, active sepsis), receiving anticoagulant therapy and/or antiplatelet drugs within last two weeks before sample, refusal to give assent.

Peripheral blood samples were collected without using a tourniquet on a citrated tube and were transferred to the laboratory with an ice-bag. The tubes were centrifuged at 2,150 X g at 4ºC for 15 min. Plasma was collected and stored at -80ºC until the test time. VWF antigen level was measured using ELISA (enzyme-linked immunosorbent assay) technique.

***Ethical Consideration*:**

An approval of the study was obtained from Mansoura University Academic and Ethical Committee. Every patient signed an informed written consent for acceptance of the operation. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

The collected data were coded, processed and analyzed using the SPSS (Statistical Package for Social Sciences) version 22 for Windows® (IBM SPSS Inc, Chicago, IL, USA). Data were tested for normal distribution using the Shapiro Walk test. Qualitative data were represented as frequencies and relative percentages. Chi square test ($\chi 2$) to calculate difference between two or more groups of qualitative variables. Quantitative data were expressed as mean ± SD (Standard deviation). Independent samples t-test was used to compare between two independent groups of normally distributed variables (parametric data). P value < 0.05 was considered significant.

RESULT

Table (1) demonstrates that there were no statistically significant differences among both groups (cases versus control) regarding all the demographic characters (age, sex, body weight and height) **(P>0.05).**

Table (1): Demographic features of the studied groups:

Demographic features	Studied groups		Test of significance	P value*
	Cases (n = 20) N (%)	Controls (n = 20) N (%)		
Age				
< 1 year	2 (10%)	1 (5%)		
1 – 5 years	3 (150%)	3 (15%)	Monte Carlo	
6 – 10 years	6 (30%)	11 (55%)	test	0.463
>10 years	9 (45%)	5 (25%)		
Sex				
Male	8 (40%)	10 (50%)	χ^2= 0.404	0.525
Female	12 (60%)	10 (50%)		
Body weight (Kg.) Mean ± SD	35.6 ± 19.5	25.7 ± 12.5	Z = -1.569	0.117
Height (cm.) Mean ± SD	128.9 ± 32.9	118.6 ± 24.9	t = 1.118	0.271

χ^2 for Chi square test Z for Mann Whitney test t for independent t test

∗ P value significant if ≤ 0.05

Table (2) demonstrates the clinical features of the studied patients. Regarding the etiology, the percentage of biliary atresia, autoimmune hepatitis, congenital hepatic fibrosis, HCV, and others were 20%, 20%, 15%, 10 and 35% respectively. The percentages of fibrotic stages were 30 %, 35 % and 35 % for mild, moderate and severe fibrosis respectively. The majority of cases (85%) had no ascites, with only one case (5%) developed mild ascites and two case developed moderate ascites (10%). Varices was proved to be present in half of the cases (50%), while hepatosplenomegaly was developed in ¼ of cases.

Table (2): Clinical features of the studied patients:

Clinical features	Studied patients (n = 20) N (%)
Etiology of liver disease	
Biliary atresia	4 (20%)
Autoimmune hepatitis	4 (20%)
Congenital hepatic fibrosis	3 (15%)
HCV	2 (10%)
Others	7 (35%)
Fibrosis stage	
Mild	6 (30%)
Moderate	7 (35%)
Severe	7 (35%)
Ascites	
No ascites	17 (85%)
Mild	1 (5%)
Moderate	2 (10%)
Severe	0
Varices	
Yes	10 (50%)
No	10 (50%)
Hepatosplenomegaly	
Yes	5 (25%)
No	15 (75%)

Table (3) demonstrate the values of vWF among the studied groups. There was highly statistically significant increase in vWF value in the cases compared to the controls (167.1 ± 47.8 Vs 112.9 ± 36.1) **(P<0.001).**

Table (3): Values of vWF (IU/dL) among the studied groups:

Study groups	vWF Ag				P value*
	Mean ± SD	95% CI of the mean	IQR	Median	
Cases (n = 20)	167.1 ± 7.8	144.8 – 189.6	38.0	181.5	t = 4.050 P <0.001
Controls (n = 20)	112.9 ± 6.1	96 – 129.8	65.6	113.1	

t for independent t test * P value significant if ≤ 0.05

Table (4) illustrate vWF Ag values in patients with fibrosis by their clinical features. vWF Ag values demonstrated insignificant differences concerning etiology of liver disease, presence or absence of ascites and hepatosplenomegaly **(P>0.05).**

On the contrary, Values of vWF Ag were demonstrated to be significantly increases in cases with severe fibrosis as well as cases with varices **(P<0.05).**

Table (4): Values of vWF Ag (IU/dL) in patients with fibrosis by their clinical features:

Clinical features	vWF Ag (Mean ± SD)	Test of significance	P value*
Etiology of liver disease Biliary atresia Autoimmune hepatitis Congenital hepatic fibrosis HCV Others	 158.3 ±57.1 200.2 ± 11.3 172 ± 16.5 183.4 ± 27.4 146.7 ± 62.9	F = 0.873	0.503
Fibrosis stage Mild Moderate Severe	 111.8 ± 53.9 178.9 ± 5.7 202.9 ± 8.3	F = 15.854	P1 = 0.003 P2 <0.001 P3 = 0.449
Ascites Yes No	 201.5 ± 15.6 161.1 ± 49.2	t = 1.380	0.185
Varices Yes No	 190.1 ± 17.9 144.3 ± 57.8	t = 2.393	0.028
Hepatosplenomegaly Yes No	 196.5 ± 13.5 157.4 ± 51.4	t = 1.655	0.115

F for one way ANOVA test t for independent t test ∗ P value significant if ≤ 0.05

P1 for comparison between mild and moderate fibrosis, P2 for comparison between mild and severe fibrosis, P3 for comparison between moderate and severe fibrosis.

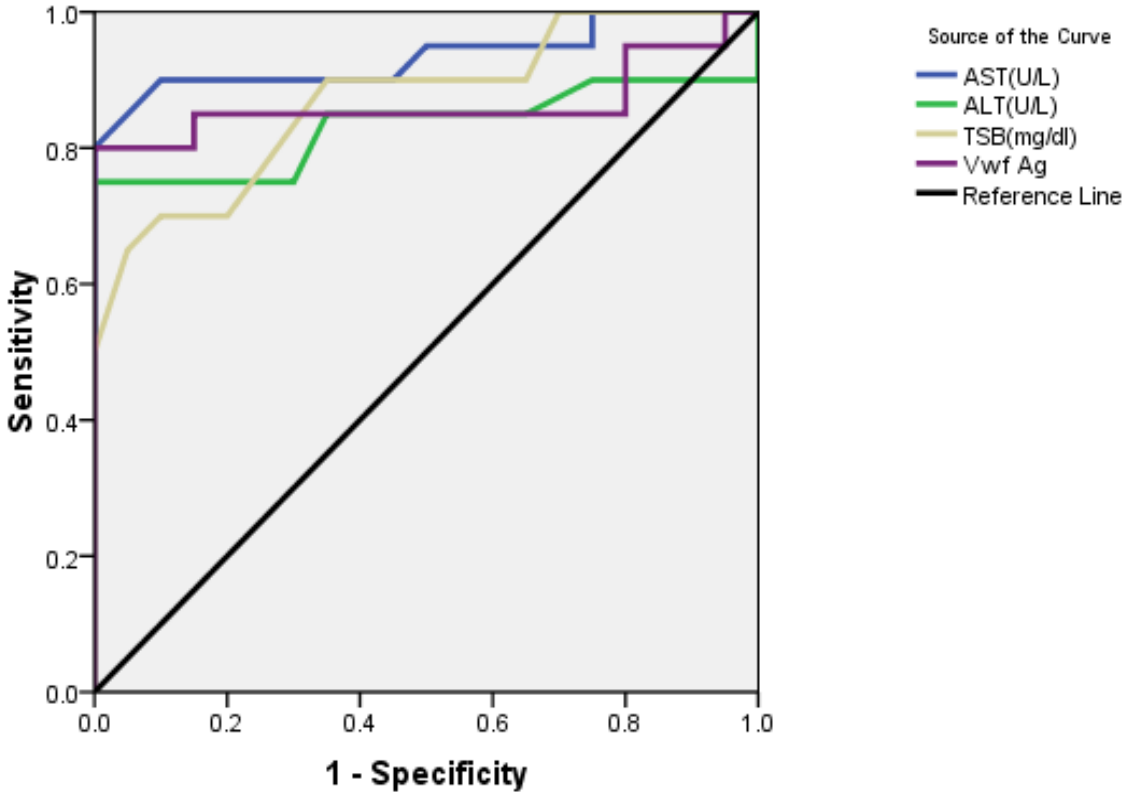
Table (5) display that vWF could be used as a significant predictor for liver fibrosis**(P<0.001)** at all cut off values with sensitivity ranging from 85% to 80%, specificity ranging from 85% to 80%, PPV ranging from 81% to 85%, NPV ranging from81% to 85% **(AUC=0.865).**

Table (5): vWF as a predictor for liver fibrosis:

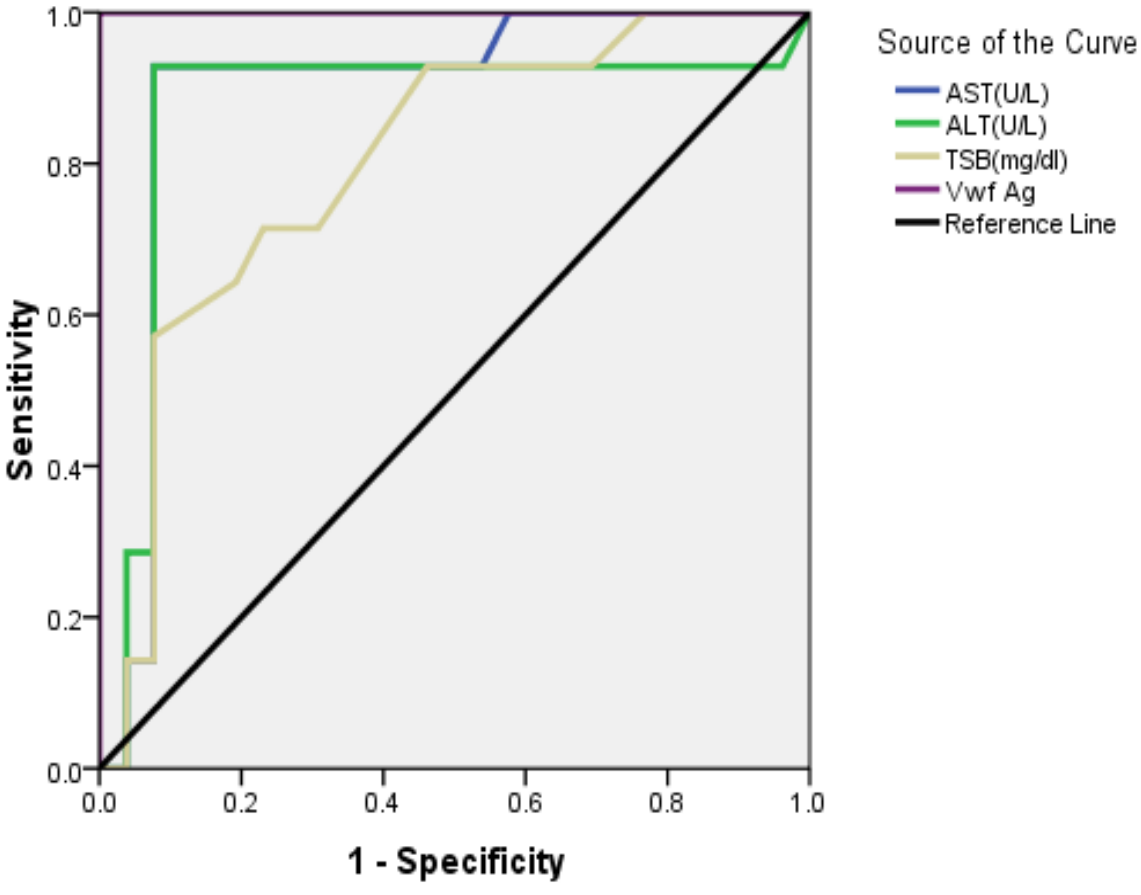
Test	Cutoff	Sensitivity %	Specificity %	PPV %	NPV %	AUC	P value*
vWF (µg/ml)	150.5	85	80	81	84.2	0.865	<0.001
	152	85	85	85	85	0.865	<0.001
	153.5	80	85	84.2	81	0.865	<0.001

* Significant; PPV, Positive predictive value; NPV, Negative predictive value; AUC, Area under curve.

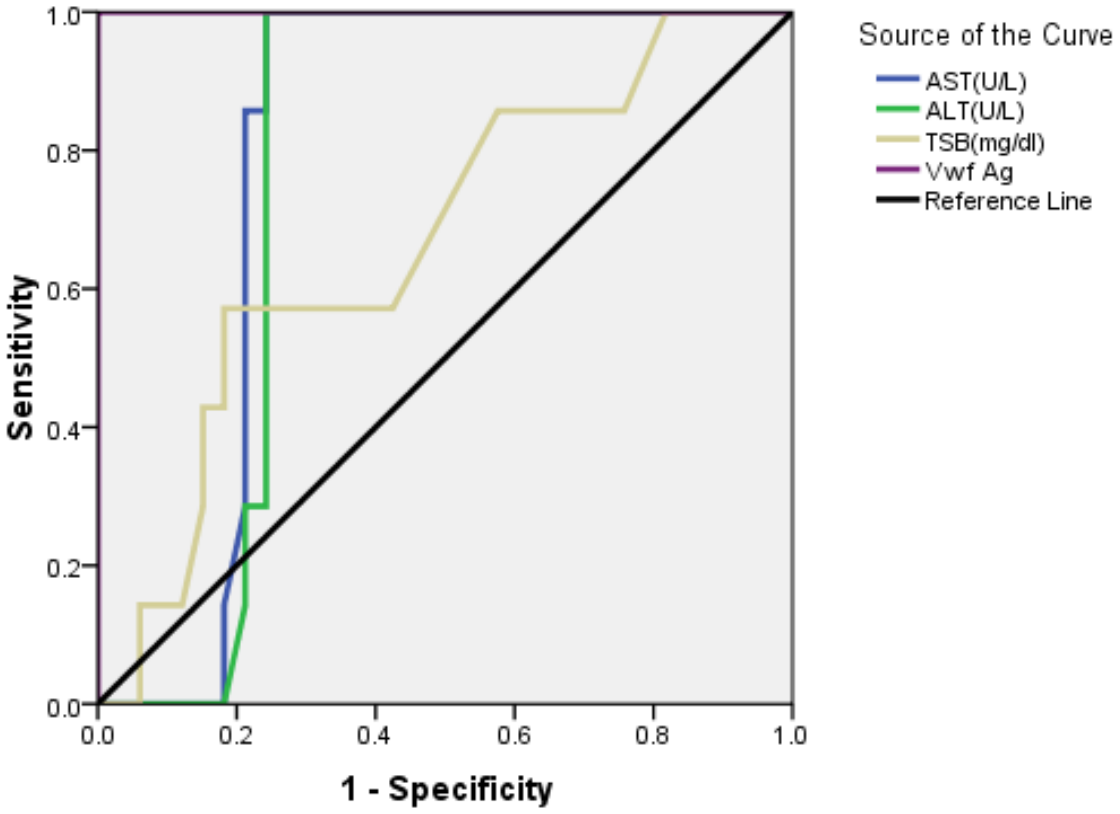
Figure (1 A, B, C) demonstrate the AUCs for different laboratory tests throughout the different groups of fibrosis. AUC for Control vs. mild, moderate and severe fibrosis were 0.934, 0.832, 0.870 and 0.865 for AST, ALT, TSB and vWF-Ag respectively. AUC for Control, mild vs. moderate, severe were 0.894, 0.870, 0.802 and 1.000 for AST, ALT, TSB and vWF-Ag respectively. AUC for Control, mild, moderate vs. severe were 790, 0.768, 0.669 and 1.0 for AST, ALT, TSB and vWF-Ag respectively.



(A) Control vs. mild, moderate and severe fibrosis



(B) Control, mild vs. moderate, severe.



(C) Control, mild, moderate vs. Severe

Figure (1): The results of the different AUCs fordifferent laboratory tests throughout the different groups of fibrosis.

Table (6) illustrated that there were highly statistically significant correlations between vWF Ag level and both fibrosis stage and Child Score among the studied patients **(P≤0.001).**

Table (6): Correlations between vWF Ag level and different parameters in the studied patients:

Clinical parameter	vWF Ag level	
	rho	P value
Fibrosis stage	0.943	<0.001
Child Score	0.945	0.001

rho for spearman correlation, P value significant if ≤ 0.05

If rho ≤0.5= weak correlation, If rho >0.5= strong correlation

DISCUSSION

In terms of the demographic features (age, sex, body weight and height), both studied groups demonstrated insignificant differences. Such fact indicated that demographic characters were not interfering with the net results of the study.

Concerning the cause of liver cirrhosis among the studied cases, biliary atresia (20%) and autoimmune hepatitis (20%) were the most common causes followed by congenital hepatic fibrosis (15%) and lastly HCV (10%) (7% other causes).

Although rather uncommon and multifactorial in etiology, liver cirrhosis is a severe and often rapidly fatal disease in pediatric patients. There is little epidemiological information regarding etiology of liver cirrhosis in children and it is changed over time [13].

In the same line, a Japanese study conducted by **Tanaka *et al.*** [14] revealed that the main causes of liver cirrhosis in children who underwent liver transplantation were biliary atresia (72.9%), cryptogenic (8.1%), Budd Chiari syndrome (5.4%), progressive familial intrahepatic cholestasis (5.4%), and lastly Wilson disease (2.7%).

Similarly, a Brazilian study conducted **Ferreira *et al.*** [15] by revealed that, the most common causes of pediatric fibrosis were biliary atresia (50%), autoimmune disorders (20.5%) and cryptogenic (17.6%).

In addition, in Oman, progressive familial intrahepatic cholestasis (30%) and fibrocystic diseases of the liver and kidneys (21%) were the most common causes of liver fibrosis [16].

These reports from developing countries recognized that metabolic disorders, cholestatic syndromes and autoimmune hepatitis were the most common causes of fibrosis in children in these countries. Thus, geographical was demonstrated to be the most contributing factor that interfering with the cause of liver fibrosis [13].

The majority of cases (85%) had no ascites, with only one case (5%) developed mild ascites and two case developed moderate ascites (10%). Varices was

demonstrates to be present in half of the cases (50%), while hepatosplenomegaly was developed in ¼ of cases.

In accordance, **Dehghani *et al.*** [13] displayed that, the most frequent complications of liver cirrhosis in children were jaundice (67.9%), ascites (44.3%), gastrointestinal variceal bleeding (16.1%), and hepatic encephalopathy (12.7%)**.**

There was highly statistically significant increase in vWF value in the cases compared to the controls (167.1 ± 47.8 Vs 112.9 ± 36.1, IU/dL) (P<0.001). In addition, vWF Ag values demonstrated insignificant differences concerning etiology of liver disease, presence or absence of ascites and hepatosplenomegaly (P>0.05). On the contrary, values of vWF Ag were demonstrated to be significantly increases in cases with severe fibrosis as well as cases with varices (P<0.05).

Several mechanisms have been proposed to explain the increase of vWF in fibrosis, including endothelial cell damage as a result of bacterial-derived products promoting endothelial secretion of vWF, expanded endothelial surface due to collateralisation and angiogenesis [8]**,** and reduced clearance of vWF, possibly due to the reduced levels of the cleaving protease ADAMTS [17]**.**

For example, chronic liver disease (CLD) with portal hypertension promotes bacterial translocation and subsequent inflammation leading to endothelium activation [18]**.**

There is increasing evidence that the deregulated inflammatory response in advanced fibrosis itself further aggravates portal hypertension in a vicious circle and despite an overall correlation of the hepatic venous pressure gradient (HVPG) with vWF [19]**.**

Of note, vWF is released by activated endothelial cells and therefore represents an indicator of endothelial cell activation and plays a crucial role in high shear stress depending on primary hemostasis. The endothelium plays a crucial role in many vascular diseases and endothelial dysfunction is a fundamental component of the increased hepatic vascular tone of fibrotic livers [7]**.**

Activation of thrombocytes and endothelium finally leads to platelet aggregation and, probably, to microthrombotic events. Those events lead to increased portal pressure and furthermore might lead to worsening of fibrosis. As vWF is elevated in liver disease, it might be a key player in establishing liver fibrosis [20]**.**

These results indicate that VWF Ag is possibly associated with liver fibrosis progression. Thus, VWF Ag should be used in combination with conventional biomarkers and/or parameters for diagnosing severe liver fibrosis stage as their combination may increase the diagnosability of liver fibrosis stages [14]**.**

This came in agreement with **El-Toukhy and Issa** [21] who conducted their study on sixty two patients with liver cirrhosis, divided into two groups according to presence (group I) or absence (group II) of varices. In addition, twenty healthy persons served as control group (group III).They displayed that, Receiver operating characteristics (ROC) curve analysis of vWF revealed that, vWF at cutoff value of 173.8 µg/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%; area under the curve was 86.6. In addition, there was significant positive correlation between vWF and esophageal varices grade as well as severity of portal hypertensive gastropathy. Thus, they revealed that, vWF is a good predictor for development of esophageal varices.

In the same line, **We *et al.*** [22] demonstrated that, cutoff values of vWF (1414 mU/ml and 1990 mU/mL, PPV 90.3% and 86.3%, respectively) were provided to detect the presence and degree of esophageal varices**.**

Similarly, **Takaya *et al.*** [23] displayed that, the VWF: Ag levels were higher in patients with severe liver fibrosis stages than in those without (185.3 ± 95.2 versus 129.6 ± 87.4).

These results are comparable to those reported by **Ferlitsch *et al.*** [11] who reported that, VWF values were higher in patients with esophageal varices and history of ascites, compared to patients without, higher vWF levels were significantly associated with varices Odds Ratio (OR) = 3.27; P<0.001) and ascites (OR = 3.93; P < 0.001). In addition, they demonstrated that, the most important finding of their study is that a vWF cutoff at 315 can clearly stratify patients with compensated and decompensated liver cirrhosis.

Regarding varices, a recent Egyptian study conducted by **Abdelmaksoud *et al.*** [24] demonstrated that, VWF rise significantly in patients with esophageal varices (169.3±20.2 in cases vs 146.8±35.5 µg/dL in the controls p<0.001). Thus, the demonstrated that, such marker can be reliable in prediction of the presence of EV. In addition, VWF Ag can be reliable marker in prediction of risky and bleeding varices.

The current study demonstrated that, vWF could be used as a significant predictor for liver fibrosis (P<0.001) at all cut off values with sensitivity ranging from 85% to 80%, specificity ranging from 85% to 80%, PPV ranging from 81% to 85%, NPV ranging from 81% to 85% (AUC=0.865).

In the same line, **El-Toukhy and Issa** [21] demonstrated that, vWF is a good predictor for the development as well as the prognosis in patients with cirrhosis.

In addition, **Maieron *et al.*** [25] reported that, the diagnostic performance of vWF predicting liver fibrosis in comparison to other fibrosis scores was analysed by AUROC: with 0.703, vWF is one of the best markers to differentiate patients with fibrosis (F1-F4) from patients without fibrosis (F0). They concluded that, vWF offer an easy possibility to evaluate the stage of fibrosis to diagnose subclinical cirrhosis in patients with chronic hepatitis C.

Similarly, **Takaya *et al.* [14]** concluded that, VWF is a potentially useful biomarker to diagnose severe liver fibrosis and predict HCC development. The area under the curve of VWF: Ag for diagnosis of severe liver fibrosis stage was 0.721.

The current study demonstrated that, there were highly statistically significant correlations between vWF Ag level and both fibrosis stage and Child Score among the studied patients **(P≤0.001).**

Similarly, **El-Toukhy and Issa [21]** displayed that; there was a significant positive correlation between vWF and Child as well as MELD scores.

These results are comparable to those reported by **Lisman *et al.* [8]** who reported that, when patients were classified according to MELD score, they also observed a strong correlation between vWF levels and severity of the disease as assessed by the MELD score ($r= 0.448$, $P<0.001$).

They also reported that, they added vWF levels were substantially elevated in Child A (488%), child B (711%) and child C (735%) cirrhosis, where in the reference group, the median vWF propeptide levels was 89% ($p<0.001$). They added, there was positive correlation between vWF and Child classification **[8].**

CONCLUSIONS

It could be concluded that Willebrand factor antigen level was positively correlated with liver function tests as well as varices and could be used as a significant predictor to severity of liver fibrosis and / or cirrhosis in children and infants with chronic liver disease.

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