



ORIGINAL RESEARCH ARTICLE

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# Role of plasma von Willebrand factor antigen in prediction of esophageal varices in pediatric and adolescent patients with portal hypertension

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## Abstract

**Background:** Ruptured esophageal varices (EVs) are a leading cause of death in Portal hypertension (PHT), it has been a big concern of research to screen EVs through non-invasive approaches. This study aimed to evaluate the role of plasma von Willebrand factor antigen (VWF-Ag) assay for early detection of EVs in patients with portal hypertension. This was a cross-sectional study, done on 47 portal hypertensive children and adolescents who were collected from the Pediatrics Hepatology Clinic, Children Hospital, Ain Shams University. All patients were subjected to comprehensive history taking, thorough clinical examination, routine investigations, abdominal ultrasound, upper GI endoscopy, and measurement of plasma VWF-Ag level. The patients were divided based on their endoscopic findings into two groups; a varices group which included 37 patients, and a non-varices group which included 10 patients.

**Results:** VWF-Ag rise significantly in patients with EVs, revealing a direct positive association with the degree of EVs.

**Conclusion:** The plasma VWF-Ag can be applied as a non-invasive evidence of the presence and grading of EVs.

**Keywords:** Portal hypertension, von Willebrand factor antigen, Esophageal varices

## Background

Portal hypertension (PHT) is an extremely dangerous consequence of liver cirrhosis with its effects, e.g., hepatorenal syndrome, hepatic encephalopathy, ascites, and varices [1].

Ruptured esophageal varices (EVs) are a main cause of mortality in patients with liver cirrhosis and 30% may experience as a minimum one episode of variceal hemorrhage within a year of detection of varices [2].

So, searching for its markers is a matter to be considered carefully, as it might help in early detection, early treatment, or prevention of the progression of the condition [3].

VWF is a big multimeric protein with a vital function in the hemostasis process, as proven by the serious hemorrhage tendency combined with entire VWF insufficiency [4]; on the other hand, higher values of VWF are linked to thrombosis in arteries [5].

This work aimed to compare plasma VWF-Ag levels between variceal and non-variceal groups to assess its reliability as a predictor of varices presence, in addition, to assess if plasma VWF-Ag in variceal cases directly correlates with variceal grade.

## Methods

This is a cross-sectional study that was conducted over 1 year, from December 2018 to December 2019, on pediatric and adolescent patients diagnosed with portal hypertension collected from hepatology clinic, Children Hospital, ain Shams University.

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We included 47 portal hypertensive pediatric cases (diagnosis was based on clinical, laboratory, and radiological investigations) who were divided according to endoscopic findings into two groups: (varices group: which included 37 cases with EVs, and non-varices group: which included 10 cases without EVs).

Patients older than 18 years, and those with disorders of VWF as heart failure, renal failure, acute infection on time of sampling, diabetes mellitus, hypertension, hyperlipidemia, malignancy, and patients on anticoagulant or antiplatelet therapy therapy, patients with active bleeding were excluded from the study. Written informed consent from the care giver of the participants was attained before being engaged in the study after getting approval from the Research Ethics Committee at the Faculty of Medicine.

Demographic data of the patients were recorded including age and sex, they were examined for clinical signs of liver disease and portal hypertension, size of liver, spleen, and presence of ascites. Patients were subjected to routine laboratory investigations including complete blood count, liver enzyme: alanine transaminase (ALT), aspartate aminotransferase (AST), serum alkaline phosphatase, albumin, bilirubin, international normalized ratio (INR)). Child-Pugh classification was used to classify the severity of liver disease [6].

Abdominal ultrasonography was done to detect size of liver and spleen, presence of cirrhosis, portal vein diameter [for children younger than 10 years, the normal diameter was 8.5 mm ( $\pm$  2.7). For those whose age between 10 and 20 years, the normal diameter was 10 mm ( $\pm$  2)], and presence of collaterals [7]. Moderate splenomegaly was considered if the largest dimension was 11–20 cm and marked splenomegaly if the largest dimension was more than 20 cm [8].

Upper GIT endoscopy was done using disinfected upper gastrointestinal video scope (OLYMPUS model) after good preparation of the patient. Patients were advised to fast for at least 6 h before the upper endoscopy. Complete evaluation of the esophagus, stomach and the duodenum down to the second part of the duodenum. Upper GIT endoscopy was performed in all cases to detect and grade the presence of EVs, they were graded according to the Japanese Research for Portal Hypertension Classification System as follows: grade (Gr) I: small EVs, Gr-II: moderated sized varices with slight obscuring of the gastroesophageal junction, Gr-III: large varices displaying luminal prolapse markedly obscuring the gastroesophageal junction and Gr IV: very large EVs, entirely obscuring the gastroesophageal junction and do not flattens on insufflation [9]. Portal hypertensive gastropathy was detected and categorized according to the classification proposed by

Tanoue and his associates [10] into mild, moderate, and severe.

VWF-Ag measurement using VWF-Ag ELISA: vWF: Ag detection is a sandwich ELISA through subsequent processes including dilution, incubation, washing, and quantification. It runs on the automated VIDAS® immunoanalyzers (VIDAS, Biomerieux, France). Patient vWF Ag in comparative percent intensity is settled alongside a curve based on the reference plasma provided with the kit.

### Data analysis

The collected data were coded, and analyzed using the SPSS (Statistical Package for Social Sciences) version 22 for Windows® (IBM SPSS Inc., Chicago, IL, USA). Qualitative data were signified as frequencies and relative percentages. The chi-square test ( $\chi^2$ ) was utilized to determine the difference between qualitative variables as indicated. Continuous data were expressed as mean  $\pm$  SD or median (min-max).

Independent samples *t* test was used to compare between two independent *t* groups of normally distributed variables while Mann-Whitney *U* test was used for non-normally distributed data. Comparison between three or more groups with normally distributed quantitative data was performed using the one-way ANOVA test. Pearson's correlation was used to test the correlation between two variables with parametric quantitative data. The receiver operator characteristic (ROC) curve was tested to calculate the diagnostic ability of quantitative variable (Von Willebrand factor) in the prediction of categorical outcome (varices). For all the above-mentioned tests, the level of significance was expressed as the probability of (*p* value) and the results were explained as following: non-significant if the *p* value is  $>$  0.05, significant if the *p* value is  $\leq$  0.05, highly significant if the *p* value  $<$  0.001.

## Results

### Demographic data

The mean age of the included cases was 8.5 and 7.5 years in the non-varices and varices groups, respectively. Six males and four females were included in the non-varices group, whereas the other group had 27 males and 10 females. Both ages, gender, and duration of the disease were statistically insignificant between the two groups, most recruited patients have classified as class A Child-Pugh score, with no significant difference between the two study groups (*p* = 0.911). The variceal group was receiving significantly higher doses of Inderal compared to the non-variceal group (*p* = 0.001).

**Table 1** Analysis of laboratory parameters in the two groups

	Groups		Test of significance	P
	No varices (N = 10)	Varices (N = 37)		
Total serum bilirubin (mg/dl)	0.6 (0.2–6.3)	0.4 (0.1–8.6)	$z = -1.503$	0.137
Hemoglobin (gm/dl)	9.89 ± 1.05	9.56 ± 1.71	$t = 0.264$	0.527
WBCs (10 <sup>6</sup> /ml)	5.85 (4.3–9.1)	4.6 (2–11.6)	$z = -1.209$	0.231
PLTs(10 <sup>6</sup> /ml)	159.5 (74–273)	105 (62–492)	$z = -0.702$	0.497
ALT (U/L)	29 (10–46)	19 (10–221)	$z = -0.247$	0.808
AST (U/L)	45.5 (28–83)	41 (17–311)	$z = -0.507$	0.612
Albumin (g/dl)	3.78 ± 0.61	3.78 ± 0.43	$t = 0.010$	0.992
PTT	31.21 ± 5.41	30.94 ± 7.37	$t = 0.109$	0.914
INR	1.31 ± 0.24	1.27 ± 0.25	$t = 0.422$	0.675
Serum creatinine (mg/dl)	0.4 (0.1–0.8)	0.4 (0.1–0.6)	$z = -0.093$	0.929

Continuous data expressed as mean ± SD or median (min–max)

P probability

T = independent samples t test

Z = Mann-Whitney test

**Laboratory parameters**

CBC, liver functions, and renal functions were not significantly different between the two groups ( $p > 0.05$ ) (Table 1).

**Ultrasonographic findings**

Liver size was not significantly different between the two groups ( $p = 0.104$ ). However, marked splenic enlargement was significantly more observed in the variceal group ( $p < 0.001$ ) (Table 2).

Endoscopic findings: In this study, variceal grades among the variceal group were as follows; grade I (13.5%), grade II (32.4%), grade III (37.8%), and grade IV (16.2%). There was a significant difference between the two groups regarding PHG ( $p = 0.035$ ). Severe PHG was detected more in the variceal group (35.1%) compared to the non-varices group (10%) (Table 2).

Von Willebrand factor: VWF was significantly higher in the variceal group compared to the non-variceal cases (mean ± SD = 212.88 ± 25.53 vs. 147.65 ± 16.90%— $p < 0.001$ ) (Fig. 1). It was evident that VWF level increased as variceal grades increases ( $p = 0.003$ ) (Fig. 2) with a strong positive correlation between VWF levels and variceal grade ( $p < 0.001$ ) (Fig. 3). Using a cut-off value of 176.8%, VWF showed sensitivity and specificity of 96 and 100% respectively as a predictor of varices presence with a diagnostic accuracy was 95% (Fig. 4).

**Discussion**

Ruptured EVs resulting from portal hypertension is believed one of the main triggers of fatality in cirrhotic patients and 30% of those patients will experience an episode of variceal hemorrhage during the first year of

variceal diagnosis [11]. Various predictors for the EVs presence with different levels of precision were weighed, involving laboratory and radiological procedures [12].

Comparison between the two groups as regards their demographic, Child score revealed no significant

**Table 2** Analysis of US and endoscopic grading of portal vein gastropathy findings in the two study groups

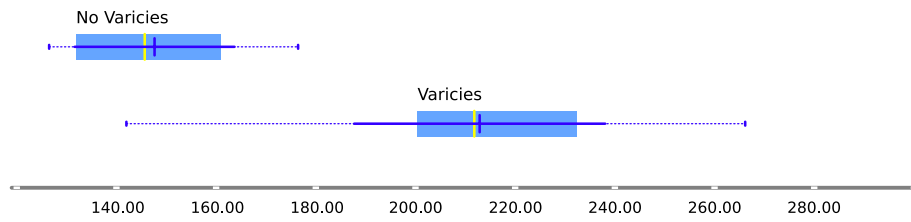
	Groups				Test of significance
	No varices (N = 10)		Varices (N = 37)		
Liver size by US					
Large	4	40%	21	56.8%	$\chi^2 = 2.006$ $P = 0.104$
Moderate	1	10%	4	10.8%	
Normal	5	40%	12	32.4%	
Spleen size by US					
Markedly enlarged	2	20%	33	89.2%	$\chi^2 = 9.352$ $P < 0.001^*$
Moderate enlarged	5	50%	3	8.1%	
Normal	3	30%	1	2.7%	
Endoscopic grading of portal vein gastropathy					
Mild	7	70%	8	21.6%	$\chi^2 = 5.631$ $P = 0.035^*$
Moderate	2	20%	16	43.2%	
Severe	1	10%	13	35.1%	
Endoscopic grading of varices					
Grade 1	–		5	13.5%	
Grade 2	–		12	32.4%	
Grade 3	–		14	37.8%	
Grade 4	–		6	16.2%	

Categorical data expressed as number (%)

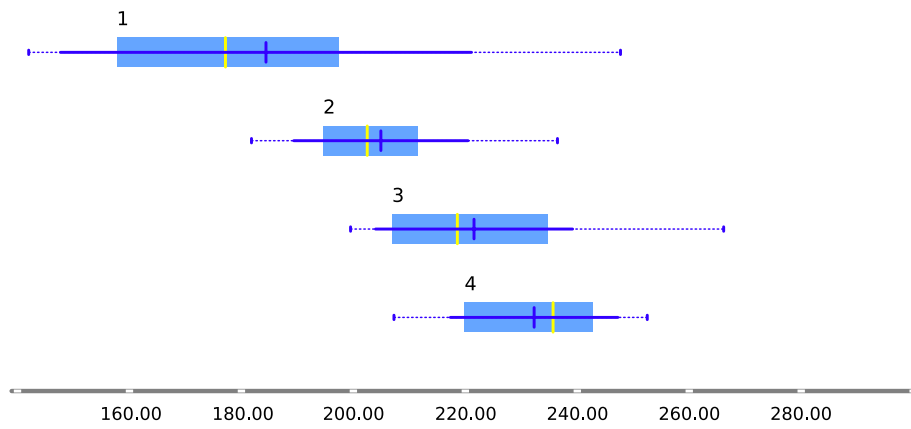
P probability

$\chi^2 =$  chi-square test

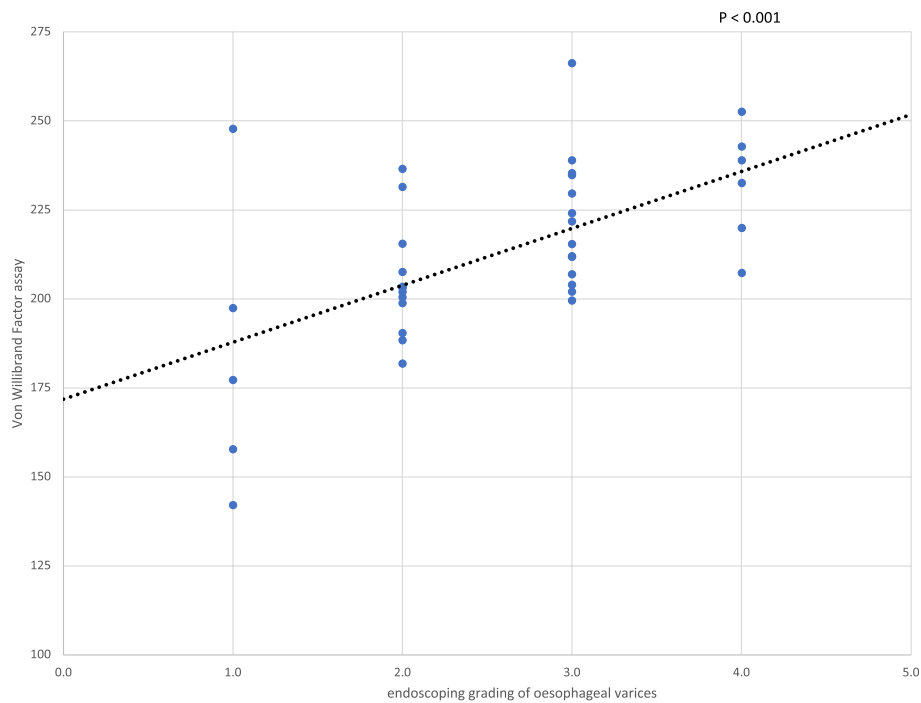
\*Statistically significant ( $p < 0.05$ )



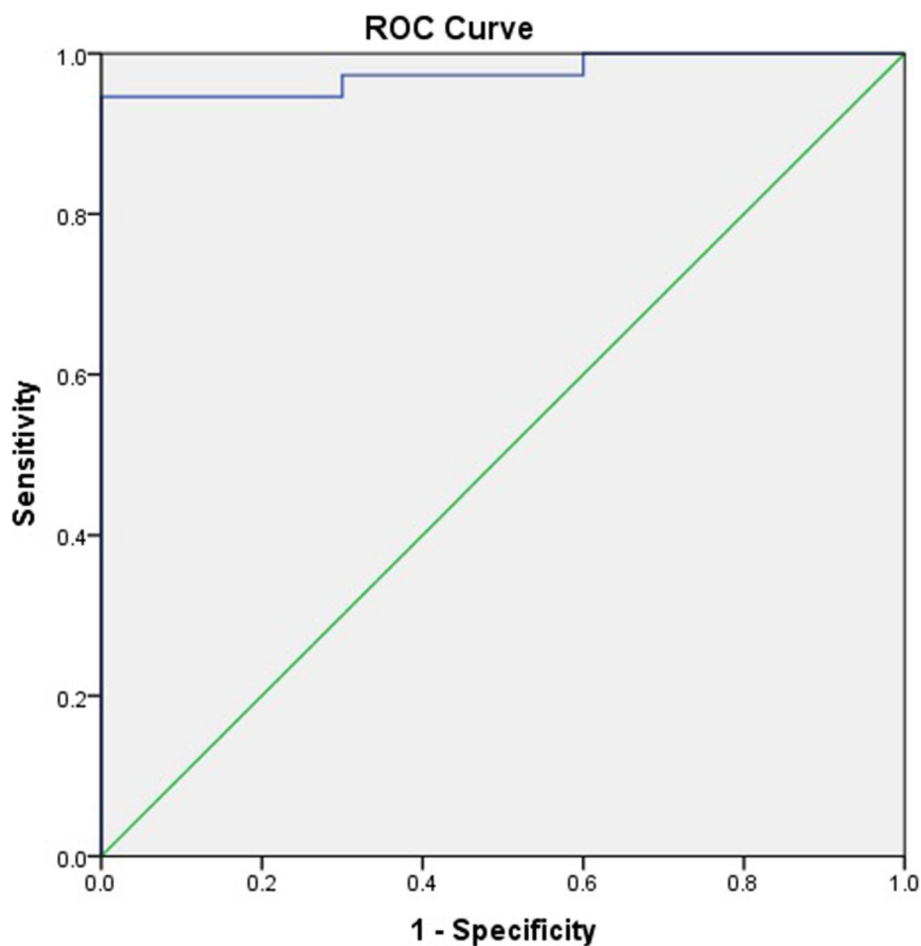
**Fig. 1** Von Willebrand factor levels between the two groups



**Fig. 2** Von Willebrand factor in different grades of varices



**Fig. 3** Correlation between variceal grade and von Willebrand factor level



**Fig. 4** ROC curve for von Willebrand factor as a predictor of variceal presence

differences as regards any of these data. This comes in favour of abolishing the effects of possible confounding factors.

As regards clinical and routine laboratory parameters no significant differences were found between the two studied groups except the spleen size, marked enlargement was diagnosed in 89.2% of cases in the variceal group, while it was present only in 20% of cases in the other group ( $p < 0.001$ ).

Another study verified the same findings, as the spleen long axis was significantly increased in the variceal group (17.9 vs 15.1 cm in no varices group— $p = 0.0012$ ) [13]. Also, Agha et al. [14] stated that a greater mean spleen span was noticed in patients with varices when compared to patients without varices (14.7 cm versus 10.9 cm,  $P = 0.0006$ ). This also coincides with Kedar et al. [15] who assumed that splenomegaly (> 12 cm) may be the mere indication of high portal pressures.

As regards the occurrence of gastropathy in this study, severe gastropathy was more found in the variceal group (35.1%), but mild gastropathy was the only finding in the no varices group, with a significant difference between the two groups ( $p = 0.035$ ). Consistent with our results, an additional study described that the occurrence of PHG was more obvious in the variceal group (64.4% vs. 8.6% in the non-variceal group— $p = 0.001$ ) [9].

Coming to the level of vWF in the current study, it was significantly increased in the varices group 212.88 % when compared to 147.65% in the no varices group  $p < 0.001$ . Applying a cut-off level of 176.8%, it revealed a sensitivity of 96% and sensitivity of 100%, with an accuracy of 95% to expect the occurrence of varices. These results are supported by several adult studies that reported that vWF was significantly higher in patients with EVs, compared to patients without EVs, but with different cut off values [13, 16, 17].

In the variceal group, varices were represented as follows: grade I 13.5%, grade II 32.5%, grade III 37.8%, and grade IV 16.2%, the level of vWF antigen was significantly positively correlated with the variceal grade ( $p < 0.001$ ). Mahmoud and his associates also reported that serum VWF was also positively correlated with variceal grade and size. It had a mean level of 1.635, 2.50, and 3.216 in cases with grades I, II, and III, respectively. Furthermore, it had a mean of 1.453 and 2.858 in cases with small and large varices respectively ( $p < 0.001$ ) [16], this comes in line with our results.

The high levels of vWF in cirrhosis may be owing to stimulation of vWF production in the cirrhotic liver [18], or decreased liver-facilitated removal due to reduced level or activity of vWF-Ag splitting protease that can lead to additional elevation of VWF-Ag levels in cirrhotic patients complicating with PHT [19].

The preceding studies recommend that a cirrhotic liver could add to the elevated VWF, but in this study, most of recruited PHT patients were from the child a, and b classification who also showed increased VWF, this could be simplified as in normal conditions VWF is eliminated from the circulation at the levels of liver and spleen. The shifting of blood via portal-systemic collaterals causes increasing the levels of such factor [20].

Additional research indicates that vWF is implicated in the formation of blood vessels, that could clarify why certain people with vWF disease have vascular malformations mainly in the gastrointestinal system which may bleed terribly [21].

## Conclusion

Based on the results of the current study, VWF-Ag can be used as a non-invasive neutral predictor for the discovery of EVs. Besides, it can be used to predict the variceal grade.

## Limitation of this study

The main limitation of this study is that it included comparatively small sample size. Correlation between VWF level in different etiologies of portal hypertension and its relation to portal hypertensive gastropathy might be another limitation.

## Abbreviations

PHT: Portal hypertension; VWF-Ag: Von Willebrand factor antigen; PV: Portal vein; EV: Esophageal varices; Gr: Grade; PHG: Portal hypertensive gastropathy; EVL: Endoscopic variceal ligation; CBC: Complete blood count; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; ELISA: Enzyme-linked immunosorbent assay.

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Not applicable.

## Authors' contributions

LE designed and directed the study. AA and KA conducted the study and analyzed the data. DR contributed to the pathological studies and interpretation of the results LE, AA, and KA wrote the manuscript. All authors have read and approved the final manuscript.

## Funding

Not applicable.

## Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## Declarations

### Ethics approval and consent to participate

Written informed consents were obtained from the parents of participating children, also ethical approval was obtained from the Research Ethics Committee at the Faculty of Medicine, Ain Shams University Hospital (FWA000017585) in the Declaration of Helsinki (FMASU REC) The study was approved in October 2016 by pediatric department committee.

### Consent for publication

Not applicable.

### Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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