

Urinary Vascular Endothelial Growth Factor (VEGF) as a Novel Marker for Early Prediction of Esophageal Varices in Patients with Chronic Liver Disease

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Abstract

Background/Aims: Vascular Endothelial Growth Factor (VEGF) has a crucial role in portal hypertension and collateral vessels formation. This study aims to assess urinary VEGF in cirrhotic patients as a predictor of presence of esophageal varices, and variceal bleeding. **Settings and Design:** 42 cirrhotic patients were randomly selected and classified into 2 groups according to the presence of variceal bleeding. **Methods and Material:** Urinary VEGF was measured and corrected against urinary creatinine. Platelet count, liver functions, abdominal ultrasonography and upper endoscopy were done. **Statistical Analysis Used:** Comparison was done by Mann Whitney and Kruskal Wallis tests. Correlation was done using Spearman rank correlation. Multivariable logistic regression was done to identify predictors of variceal bleeding and presence of large varices. Receiver operator characteristic curve (ROC) analysis was used to determine the optimum cut off value of predictors. **Results and Conclusions:** Urinary VEGF was lower in cirrhotic patients with esophageal varices than those without. Low VEGF, low platelet count and splenomegaly were found to be independent predictors of both the presence of large esophageal varices, and variceal bleeding. Cut-off values for platelet count $\leq 166.3 \times 10^3/\mu\text{L}$, and corrected VEGF ≤ 59.12 pg/mg were predictive of large esophageal varices with 93.1%, 86.2% sensitivity and 74.5%, 58.2% specificity respectively. While variceal bleeding could be predicted at a platelet count $\leq 153 \times 10^3/\mu\text{L}$, and corrected VEGF ≤ 45.08 pg/mg with 90.9%, 81.8% sensitivity and 72.6%, 59.7% specificity respectively. The study concludes that urinary VEGF can be used as an alternative to upper endoscopic screening.

Keywords

Liver Cirrhosis, Portal Hypertension, Esophageal Varices, VEGF, Variceal Bleeding

1. Introduction

Cirrhosis is the final outcome of chronic liver disease. Fibrosis, loss of normal architecture and formation of nodules essentially result in portal hypertension due to increased intrahepatic resistance [1]. The most commonly fatal complication of portal hypertension is bleeding esophageal varices [2].

Almost half of patients with liver cirrhosis have got gastro-esophageal varices at first presentation. This percentage increases with progression of liver disease. Variceal bleeding occurs at a rate of 5% - 15% per year in untreated subjects, with a mortality rate of 20% - 30%. Surveillance by upper endoscopy for the presence of varices is therefore recommended at diagnosis of liver cirrhosis to decrease mortality [3]. Follow-up is done according to presence or absence of varices, every 1 - 2 years and 2 - 3 years respectively. Upper endoscopy remains the gold standard for screening; it has its own limitations. It causes a significant burden and cost to endoscopy units and to target patients [4].

Therefore, there is a great need to develop a test to predict the presence of varices by non-endoscopic methods. Such a screening test should be simple, quick, reproducible, and cost effective. Several studies have evaluated the non-invasive markers of oesophageal varices in patients with cirrhosis, such as the platelet count, Fibro Test, spleen size, portal vein diameter, transient elastography of the liver and transient elastography of the spleen [5].

Vascular endothelial growth factor (VEGF) is a glycoprotein that selectively induces endothelial proliferation, angiogenesis, and capillary hyper-permeability and is known as a key regulator of blood vessel growth [6].

Angiogenesis in the splanchnic area is pathogenetic in causing a hyperdynamic circulation and maintaining portal hypertension. This is stimulated by multiple angiogenic factors, the main regulator of which is the vascular endothelial growth factor (VEGF) [7]. Investigations are necessary for assessment of the potential role of VEGF in early prediction of esophageal varices in patients with liver cirrhosis.

The aim of this work was to study the value of VEGF and other variables as platelets count, endoscopic findings and ultrasonographic findings in predicting the risk of upper gastro-intestinal bleeding.

2. Methods

2.1. Population of Study

This study is conducted on 42 subjects presented to emergency unit, inpatient and outpatient units at Internal Medicine Department of Cairo University Hospitals in the period of time from July, 2015 to December, 2015. The study also included 42 healthy controls, age and sex matched.

All patients with established diagnosis of liver cirrhosis were consecutively included into the study. Patients with other factors known to elevate VEGF levels were excluded. These included patients with hepatocellular carcinoma, or other solid tumors or metastasis, patients with granulomatous disorders including tuberculosis and patients with diabetes or rheumatoid arthritis.

2.2. All Patients Were Subjected to the Following

- 1) Thorough history taking including personal history, presenting complain (hematemesis or not), medical history (for diabetes, malignancy or any autoimmune disease, cause and duration of cirrhosis) and history of present illness (symptoms of portal hypertension and liver decompensation).
- 2) Full physical examination including conscious level, vital data (pulse and blood pressure), complexion, ascites, splenomegaly, pleural effusion and lower limb edema.
- 3) Blood and urinary samples were collected and the following laboratory investigations were done:
 - Platelet count.
 - Total Vascular endothelial growth factor (VEGF) in urine was done using Quantikine Elisa, Human VEGF Immunoassay Kits (R & D systems). Urinary VEGF was corrected by adjustment to urinary creatinine.
 - Liver enzymes (AST, ALT, ALP, GGT).
 - Liver function tests (total protein, albumin, and bilirubin; total and direct, PT, INR).
- 4) Abdominal ultrasound and upper GI endoscopy were done to all patients.

2.3. Ethics

The study was approved by the ethical committee at our faculty. A written informed consent was obtained from all patients.

2.4. Statistics

Data were statistically described in terms of mean \pm standard deviation (\pm SD), median and range, or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using Mann Whitney *U* test for independent samples for comparing 2 groups and Kruskal Wallis test with posthoc multiple 2-group comparisons in comparing more than 2 groups. For comparing categorical data, Chi-square (χ^2) test was performed. Exact test was used instead when the expected frequency is less than 5. Correlation between various variables was done using Spearman rank correlation equation. Accuracy was represented using the terms sensitivity, and specificity. Receiver operator characteristic (ROC) analysis was used to determine the optimum cut off value for the studied diagnostic markers. *p* values less than 0.05 was considered statistically significant. All statistical calculations were done using computer program SPSS [8] (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) release 15 for Microsoft Windows (2006).

3. Results

Use During the period of study, 42 patients with liver cirrhosis presented to emergency unit, inpatient and outpatient clinic of Internal medicine department of Cairo University with different symptoms as hematemesis, melena, jaundice, encephalopathy, ascites, lower limb edema, bleeding tendency, abdominal pain

and fever, **Table 1**. The cases were classified into 2 groups according to the presence or absence of variceal bleeding, **Table 2**.

Cases with esophageal varices were furtherly divided into 2 groups according to size of varices, **Figure 1**.

There was no significant difference between patients with and without varices as regard to age and sex. However, males have higher percentages of varices (83%) than females (61%). **Table 3** shows Child Pugh classification of studied patients. **Table 4** shows laboratory findings of studied groups.

Table 1. Clinical parameters in patient groups.

Clinical Data	No Varices n = 11	Varices n = 31	P
Hematemesis	0	20	0.000
Melena	5	23	0.082
Ascites	10	23	0.403
LL edema	6	18	0.839
Encephalopathy	3	3	0.314
Fever	5	14	0.987
Jaundice	6	19	0.733
Bleeding tendency	7	15	0.491
Pleural effusion	2	8	0.610

Table 2. Classification of cirrhotic patients with and without varices according to the presence or absence of bleeding.

Number (%)	Varices		No varices	
	Bleeding	No bleeding	Bleeding	No bleeding
31 (74 %)	23 (74%)	8 (26%)	11 (26%)	6 (55%)

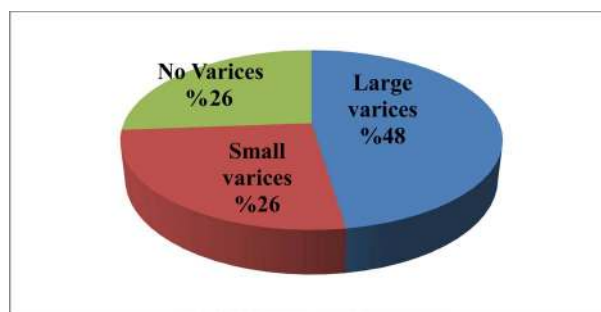


Figure 1. Cirrhotic cases classification according presence of esophageal varices and its size.

Table 3. Child Pugh classification of patients.

CHILD Pugh Class	No Varices	Varices	P
CHILD A	1	3	0.986
CHILD B	6	16	
CHILD C	4	12	

Table 4. Laboratory parameters among patient groups.

	No Varices			Varices			P
	Median	Max	Min	Median	Max	Min	
Platelets count $\times 10^3/\mu\text{L}$	119	337	44	90	182	28	0.529
AST (U/L)	55	119	15	61	456	26	0.229
ALT (U/L)	28	53	14	41	349	5	0.052
ALP (U/L)	108	690	62	92	234	52	0.258
GGT (U/L)	130	235	31	73	250	16	0.246
PT (seconds)	17	34.8	13	17	126	13	0.897
PC (%)	61	85	22	57	99	27	0.764
INR	1.4	3.6	1.2	1.49	3.3	1	0.699
Total protein (g/dl)	6.6	7.9	4.7	6.3	7.9	5	0.752
Albumin (g/dl)	2.3	4.1	1.2	2	3.4	1.1	0.455
Total bilirubin (mg/dl)	1.8	14.4	0.5	1.9	13.5	0.3	0.710
Direct bilirubin (mg/dl)	1.1	9.9	0.1	0.6	13	0	0.819
VEGF (pg/ml)	27.5	210	6	17.5	203.7	6	0.775
Urine creat. (mg/dl)	109.6	206.81	13.7	108.1	357.7	8.7	0.830
VEGF/creat ratio (pg/mg creat.)	32.02	157.3	3.7	22.65	227.6	2.9	0.368

There were no significant differences as regard to ultrasound findings of splenomegaly and ascites between patients with and without varices.

No correlation between corrected VEGF and ultrasound findings (ascites and splenomegaly) was observed. Also, no correlation between urinary VEGF; VEGF/creatinine ratio and demographic data, clinical, or laboratory parameters was found.

Median corrected urinary VEGF was significantly lower in patients with esophageal varices of any size (22.7) as compared to controls and to patients without varices (99.3 and 69.2, respectively), P-value = 0.001.

Median corrected urinary VEGF was also significantly lower in patients with large varices (17.7) as compared to patients with small or no varices (69.2), P-value = 0.001.

So VEGF levels were highest in patients without varices, lower in those with small varices and lowest in those with large varices, **Figure 2**.

Median corrected urinary VEGF was lower in cirrhotic patients with variceal bleeding than those without, and both were lower than controls, **Figure 3**. **Table 5** shows comparison of the median ranks of VEGF in the aforementioned groups.

Multivariable logistic regression showed that platelet count, urinary VEGF level and splenomegaly are independent predictors for the presence of large varices, **Table 6**. The same factors, platelet count, corrected VEGF level and splenomegaly are also independent predictors for the presence of variceal bleeding, **Table 7**.

Receiver operating characteristic (ROC) curve analysis was done to determine the optimum cut off values for platelets and urinary VEGF as predictors of the presence of large esophageal varices as well as variceal bleeding. **Figure 4** shows the optimum cut-off values with corresponding sensitivity and specificity. Panel (a) shows the sensitivity and specificity of platelet count as a marker of large esophageal

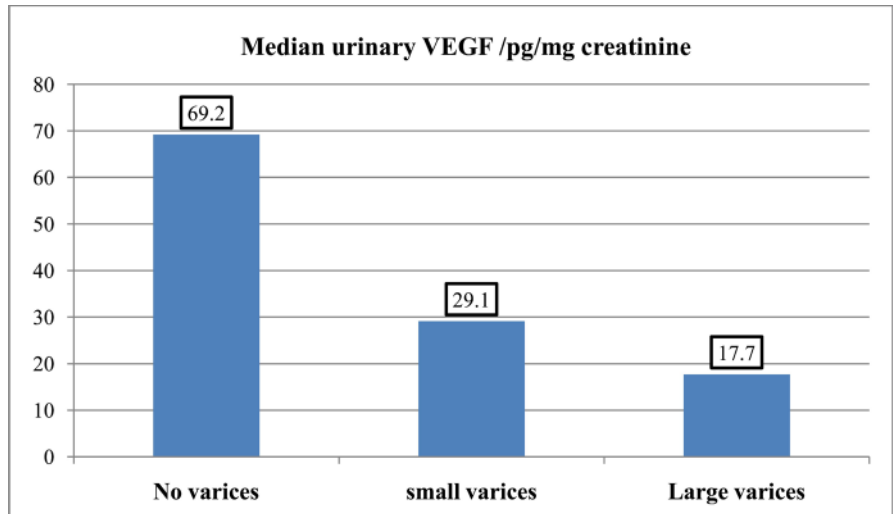


Figure 2. Corrected urinary VEGF in different groups.

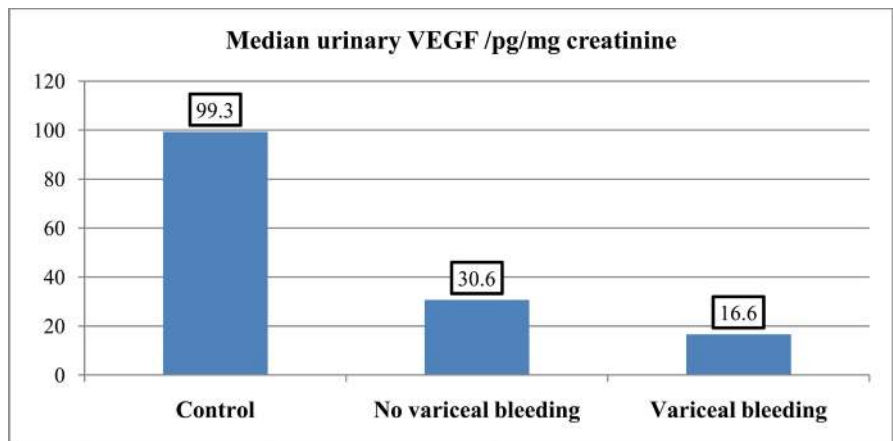


Figure 3. Median corrected urinary VEGF in patients with and without variceal bleeding, as well as healthy controls.

Table 5. Comparison of the mean rank of corrected VEGF among patients with and without variceal bleeding as well as controls.

Group	Mean rank	P
Variceal bleeding vs. controls	Control 38.05	0.000
	Bleeding 17.75	
No Variceal bleeding vs. controls	Control 37.02	0.007
	No bleeding 23.86	
Variceal bleeding vs. no Variceal bleeding	Bleeding 17.95	0.074
	No bleeding 24.73	

Table 6. Logistic Regression for predictors of large OV.

	B coefficient	P value	Odds ratio	95% CI for OR	
				Lower	Upper
PLT	-0.011	0.007	0.989	0.981	0.997
VEGF/creat	-0.014	0.046	0.986	0.972	1.000
splenomegaly	1.518	0.005	4.565	1.578	13.207

Table 7. Logistic Regression for predictors of variceal bleeding.

	B coefficient	P value	Odds ratio	95% CI for OR	
				Lower	Upper
PLT	-0.011	0.007	0.989	0.981	0.997
VEGF/creat	-0.016	0.041	0.985	0.970	0.999
splenomegaly	1.589	0.005	4.897	1.627	14.740

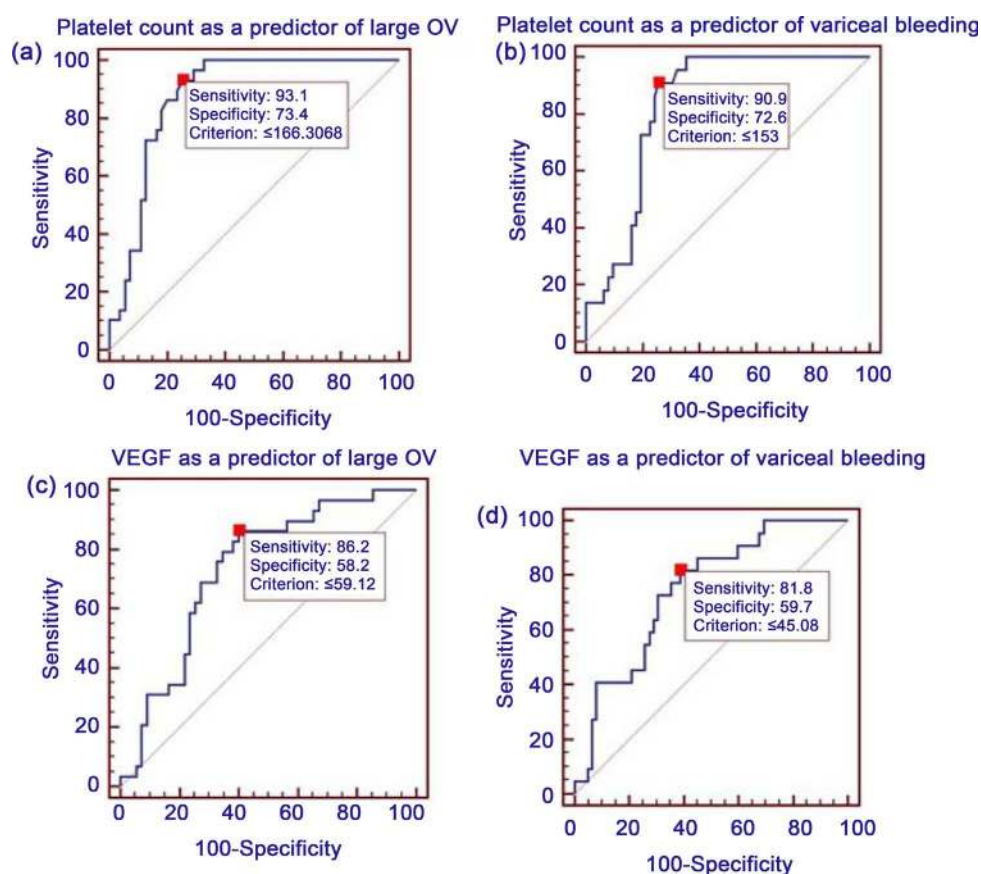


Figure 4. Receiver operating characteristic (ROC) curve analysis showing sensitivity and specificity of platelet count as a marker of large esophageal varices (a), and as a marker of variceal bleeding (b). Receiver operating characteristic (ROC) curve analysis showing sensitivity and specificity of corrected VEGF as a marker of large esophageal varices (c), and as a marker of variceal bleeding (d).

phageal varices. Area under the curve (AUC) = 0.878, P = 0.000, 95% CI 0.788 - 0.939, positive predictive value 65.8% and negative predictive value 95.3%. Panel

(b) shows the sensitivity and specificity of platelet count as a marker of variceal bleeding. Area under the curve (AUC) = 0.832, $P = 0.000$, 95% CI 0.735 to 0.905, positive predictive value 54% and negative predictive value of 95.7%.

Panel (c) shows the sensitivity and specificity of urinary VEGF as a marker of large esophageal varices. Area under the curve (AUC) = 0.734, $P = 0.000$, 95% CI 0.627 - 0.825, positive predictive value 52.1% and negative predictive value 88.8%. Panel (d) shows the sensitivity and specificity of urinary VEGF as a marker of variceal bleeding. Area under the curve (AUC) = 0.734, $P = 0.000$, 95% CI 0.627- 0.825, positive predictive value 41.8% and negative predictive value 90.2%.

4. Discussion

All patients with liver cirrhosis had significantly lower levels of corrected urinary VEGF than healthy controls. Patients with liver cirrhosis and esophageal varices had significantly lower levels of corrected urinary VEGF than those without. The study also shows that low level of corrected urinary VEGF is significantly associated with increased risk of variceal bleeding among cirrhotic patients.

Several studies had examined plasma, serum and tissue levels of VEGF as well as genetic characters of VEGF in cirrhotic patients. This study is the first to measure urinary VEGF to assess the risk of variceal bleeding in cirrhotic patients. Measuring VEGF in urine, as opposed to serum or plasma, is preferable since urine sample collection is less invasive and simple than drawing blood. In addition, venipuncture activates platelets and release cytokines, including VEGF, which artificially elevates measured VEGF level [9].

None the less, these results correlate well with similar studies measuring serum VEGF: Serum VEGF levels in cirrhotic patients were shown to be significantly lower than those of healthy controls and the mean serum level of VEGF of the cirrhotic patients with portal hypertension was significantly lower than of those without [10]. Other studies also confirmed that serum VEGF levels in patients with cirrhosis were lower than controls [11] [12] [13].

On the other hand, the study done by Nasr *et al.* in 2013, showed that serum levels of VEGF was significantly increased in cirrhotic patients compared to controls and that the levels of VEGF were positively correlated with portal vein diameter [14]. Other studies also observed increased serum VEGF in liver cirrhosis compared to healthy controls [15] [16] [17].

Another study showed no significant difference between cirrhotic patients with esophageal varices and those without regarding serum VEGF [18].

There are conflicting results concerning the serum VEGF in liver cirrhosis. The precise mechanism triggering VEGF-dependent angiogenesis in portal hypertension remains speculative, but several factors known to occur in portal hypertension, such as tissue hypoxia, cytokines, and mechanical stress have been shown to promote VEGF expression in various tissues and cell types [19]. However, decreased VEGF levels may be related to endothelial dysfunction associated with liver cirrhosis and portal hypertension pathophysiology. VEGF is required

for reconstruction of hepatic cells and sequentially participates in liver regeneration by facilitating hepatocyte proliferation as well as sinusoidal and LSFC fenestrae number and size normalization [20]. VEGF production is known to be down regulated by several substances including angiostatin, and endostatin. Thus, the low serum VEGF in these patients may be related to the increased activity of these inhibitors [10].

Our study showed as well, that thrombocytopenia is an independent risk factor for presence of large varices as well as their risk for bleeding. This is in agreement with most studies [18] [21] [22]. Cirrhosis is associated with thrombocytopenia and platelet dysfunction due to multifactorial causes occurring simultaneously such as portal hypertension induced splenic pooling and sequestration of platelets from the circulation, portosystemic shunting and gut barrier disruption which result in endotoxaemia with systemic immune activation, anti-platelet antibody production, aberrant fibrinolysis, and activation of coagulation with platelet consumption as well as decreased functional liver mass in cirrhosis which results in lower thrombopoietin levels and platelet underproduction [23].

Our study showed that no significant difference in median urinary VEGF levels was noted among the different Child-Pugh-s classes. This is in accordance with the study done by Assy *et al.* that clearly indicate that decreased serum VEGF levels did not correlate with the disease severity in patients with liver cirrhosis [10]. Also, the study done by Bai in 2008 showed that the expression of VEGF in esophagus and spleen in patients with PHT was not related to Child-Pugh score [24].

In contrary, the study done by Mathonet *et al.* in 2006 showed that VEGF was strongly correlated in cirrhotic liver tissues [25]. The highest concentrations of VEGF were observed in patients with advanced stages of liver cirrhosis, which was reflected by a positive correlation with Child-Pugh score specially score C and they suggest that VEGF might be involved in cirrhosis associated angiogenesis as well as portal hypertension [15]. Another study showed that plasma VEGF levels increase with the severity of liver impairment [26] (assessed by the Child-Pugh score and MELD classification).

Our study showed no correlation between VEGF level and clinical presentations as well as no correlation was found between VEGF urinary levels and serum albumin, platelets count and the whole biochemical liver profile. Our findings are consistent with results done by previous research [10] [27]. In another study, plasma VEGF level showed positive correlation with serum bilirubin level and platelet count [17]. Also, in study done by Poon *et al.* in 2001, there was a positive correlation between the serum VEGF level and platelet count [28]. Platelets release a variety of vasoactive substances, including VEGF, and promote angiogenesis, endothelial permeability, and endothelial growth [17].

Logistic regression was done to test for the value of VEGF and other variables in prediction of the presence of large oesophageal varices, and variceal bleeding. Low platelet count, low VEGF level and splenomegaly were found to be independently associated with variceal bleeding. The same factors *i.e.* platelet count,

corrected VEGF level and splenomegaly were found to be independently associated with the presence of large varices. The two outcomes are indeed closely related as 74% of patients with large varices had at least one episode of variceal bleeding. Therefore, the lower the level of VEGF, the higher the likelihood that a patient with liver cirrhosis will experience variceal bleeding attacks.

These results highlight the association of VEGF with the presence of varices and their tendency to bleed. Furthermore, the regression analysis shows that VEGF may be viewed as a risk factor for variceal bleeding. It may play an actual role in development of large varices and subsequent bleeding. VEGF is a powerful soluble angiogenic factor [29]. It stimulates the production of endothelial progenitor cells (EPO) from the bone marrow into the circulation. These circulating EPOs target injured endothelial surfaces. Homing of EPOs into the sites of endothelial injury occurs where they play a role in repair and regeneration of the endothelium [30]. Thus, low VEGF levels will weaken this healing power and may lead to a higher risk of bleeding.

The impact of low VEGF levels on the risk of variceal bleeding may have multiple mechanisms. In addition to increasing the development of varices and hindering endothelial regeneration, it may play a role in portal hypertension. A study by Nimer *et al.* have shown significantly lower VEGF levels in patients with portal hypertension patients, with no correlation with Child-Pugh stage [10].

Receiver operating characteristic (ROC) curve analysis was done to test for the predictive ability of each variable showing significant regression value. The relatively high negative predictive value implies that patients with urinary VEGF below the suggested optimum cut-off values are less likely to have large oesophageal varices, and are less likely to bleed as well. This can be put into consideration if prophylactic endoscopy is not desired.

Similarly, platelet count seems to have a stronger negative likelihood prediction for the presence of varices and for occurrence of variceal hemorrhage.

5. Study Limitations and Future Prospects

The controversy associated with circulating VEGF levels may be due to the existence of several isoforms (VEGF121, VEGF 165 and VEGF189) [31]. Variability in isoform levels in patients with liver cirrhosis and variceal bleeding is yet to be explored.

6. Conclusion

It is concluded from this study that low urinary VEGF/creatinine ratio, thrombocytopenia and splenomegaly are independent risk factors for presence of large esophageal varices as well as their risk for bleeding. Urinary VEGF levels can be combined to platelet count, for screening of liver cirrhosis patients, due to their high sensitivity. As it has a high negative predictive value, it can be used to prevent unneeded endoscopic screening in relevant cases. Urinary VEGF should be viewed as a novel marker for the presence of oesophageal varices and the risk of

variceal bleeding.

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