Assessment of Vascular Endothelial Growth Factor (VEGF) as a New Non-Invasive Marker for Early Prediction of Esophageal Varices in Chronic Liver Disease Patients

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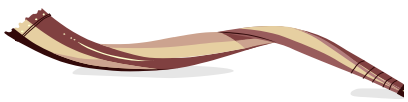

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Abstract

Background: The gold standard screening technique for presence of esophageal varices and its risk for bleeding is upper GI endoscopy. The development of a non-invasive method for early prediction of esophageal varices and its risk of bleeding would identify high-risk patients with lesser need for expensive, risky and invasive endoscopy. VEGF is known as an important angiogenic factor and has a crucial role in portal hypertension and collateral vessels formation.

Objectives: Assessment of urinary VEGF level in cirrhotic patients as a predictor of presence and severity of esophageal varices.

Methods: 42 cirrhotic patients were randomly selected and classified into 2 groups according to the presence or absence of variceal bleeding. VEGF was measured in urine of both groups and compared to 42 healthy controls. VEGF level was corrected against urinary creatinine. Platelet count, liver function tests, abdominal ultrasonography and upper GI endoscopy were done to all patients. The association between urinary VEGF and all previous parameters as well as with clinical data was sought.

Results: Significantly lower levels of urinary VEGF were detected in cirrhotic patients with esophageal varices than those without, and both groups were lower than that of controls. By multivariable logistic regression, low VEGF, low platelet count and splenomegaly were found to be independent predictors of both the presence of large esophageal varices, and variceal bleeding. Receiver operating characteristic (ROC) curve analysis showed that platelet count$\leq$ 166.3x10 ^{3}/ μL, and corrected VEGF $\leq$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 $\leq$ 153x10 ^{3}/ μL, and corrected VEGF $\leq$ 45.08 pg/mg with 90.9%, 81.8% sensitivity and 72.6%, 59.7% specificity respectively.

Conclusion: Low urinary VEGF, thrombocytopenia and splenomegaly are independent risk factors for presence of large esophageal varices as well as their risk for bleeding. These variables can be used as an alternative to upper endoscopic screening after their validation by future studies.

Key words: Liver cirrhosis, portal hypertension, esophageal varices, VEGF

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List of Abbreviations

%	Percent
°c	Degree Celsius
×g	Times gravity unit
8-iso- PGF2a	8 iso-prostaglandin F2 alpha
ADMA	Amino acid asymmetric Dimethylarginine
ALP	Alkaline phosphatase
ALT	Alanine transaminase
Anti-LC1	Anti-liver cytosol 1
AST	Aspartate transaminase
AUC	Area under the curve
A-V shunt	Arterio- Venous shunt
CD163	Cluster of Differentiation 163
CECs	Circulating Endothelial Cells
CI	Confidence interval
COOH	Carboxylic acid
CT	Computerized Tomography
CTP	Child-Turcotte-Pugh

ELISA	Enzyme linked immunosorbent assay
EPO	Endothelial progenitor cells
EVL	Endoscopic Variceal Ligation
EVO	Endoscopic Variceal Obturation
EVS	Endoscopic variceal sclerotherapy
FHVP	Free Hepatic Venous Pressure
FT	Fibro Test
g/dL	Gram /deciliter
GGT	Gama glutamate transferase
GOV	Gastroesophageal varices
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C virus
HE	Hepatic Encephalopathy
HO-1	Heme oxygenase 1
HRS	Hepato-renal Syndrome
HVPG	Hepatic Venous Pressure Gradient
IGV	Isolated gastric varice
IHVR	Intrahepatic Vascular Resistance
INR	International Normalization Ratio
ISMN	Isosorbide mononitrate

IV	Intravenous
kda	Kilo- Dalton
LC	Liver Cirrhosis
LKM-1	liver-kidney microsomal type 1
LSEC	Liver sinusoidal endothelial cell
LSM	Liver Stiffness Measurement
Max	Maximum
MELD	Model for End stage Liver Disease
mEq/L	Milliequivelant/ liter
mg	milligram
Min	Minimum
ml	milliliter
mm^3	Millimeter cubic
mmHg	Millimeter mercury
MRE	Magnetic Resonance Elastography
MRI	Magnetic Resonance Imaging
NAFLD	Non Alcoholic Fatty Liver Disease
NASH	Non Alcoholic Steato-Hepatitis
Nh_2	Amine group

nm	nanometer
NO	Nitric Oxide
NSBB	Non Selective Beta Blockers
OR	Odds ratio
OV	Oesophygeal varices
P value	Calculated probability
PC	Prothrombin concentration
Pg/mg creat.	Pecogram/milligram creatinine
PH	Portal Hypertension
PLT	Platelets
PT	Prothrombin Time
PVT	Portal Vein Thrombosis
R&D	Research and Development
ROC	Receiver operator characteristic curve analysis
SBP	Spontaneous Bacterial Peritonitis
SD	Standard deviation
SMAs	smooth muscle antibodys
TB	Tuberculosis

TE	Transient Elastography
TIPS	Transjugular intrahepatic portosystemic shunt
U/L	Unit/ liter
UGI endoscopy	Upper Gastro-Intestinal Endoscopy
U-II	Urotensin II
US	Ultrasound
VEGF	Vascular Endothelial Growth Factor
VEGFR	Vascular Endothelial Growth Factor Tyrosine kinase receptor
vs	versus
vWF	Von Willebrand factor
WHVP	Wedged Hepatic Venous Pressure
µg	microgram
µl	microliter
µm	Micrometere

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Introduction

Cirrhosis is the end stage of every chronic liver disease, resulting in formation of fibrous tissue, disorganization of liver architecture, and nodule formation, which interferes with liver function causing increased intrahepatic resistance and results in portal hypertension ***(De Franchis, 2010)***.

Portal hypertension is associated with two pathological features which are hyper-dynamic circulation and formation of porto-systemic collaterals. The opening and dilatation of collateral vessels can lead to the development of varices at various locations. Esophageal varices are one of its most common and lethal complications ***(Chan, 2009)***.

Gastro-esophageal varices are present at diagnosis in more than 50% of cirrhotic patients and it increases as liver disease progresses. Bleeding from esophageal varices occurs at a rate of 5–15% per year in untreated patients. Variceal rupture and bleeding carries a high risk of morbidity and mortality. Bleeding from esophegeal varices is associated with mortality rate of 20–30% which make it of significant clinical importance. Early diagnosis of