

# Insulin Resistance as Predictor for Esophageal Varices in Hepatitis C Virus Cirrhosis

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**Key words:**  
Oesophageal varices, ,  
Insulin resistance,  
Upper gastrointestinal  
endoscopy.

**Background and study aim :** Portal hypertension is one of the most important complications of liver cirrhosis. Endoscopic screening of all patients with liver cirrhosis would result in a large number of unnecessary additional burden to endoscopic units. This study is designed to assess insulin resistance in cirrhotic patients due to hepatitis C infection as non invasive parameter for esophageal varices.

**Patients and Methods :** This study was conducted on 50 cirrhotic patients (Child A) post hepatitis C who attended the Hepatology Department and outpatient clinic at Shebein El Kom Teaching Hospital. All the patients were evaluated by thorough history ,clinical examination, biochemical parameters ,metabolic features, including insulin resistance by

the homeostasis model assessment (HOMA), ultrasonography , liver biopsy and upper gastrointestinal endoscopy to search for esophageal varices.

**Results :** EVs (esophageal varices) were detected in 18 of 50 patients. By multivariate analysis ,the presence of EVs was independently associated with a low platelet count/spleen diameter ratio ( $562.75 \pm 99.16$ ) , a high HOMA-IR score ( $5.49 \pm 0.754$ ), high body mass index , low hemoglobin, low albumin, high alanine aminotransferase and high aspartate aminotransferase.

**Conclusion:** Insulin resistance in patients with Hepatitis C virus cirrhosis (Child A ) measured by HOMA-IR score significantly predicts the presence esophageal varices in this patients and can be used as non-invasive parameter for predicting esophageal varices.

## INTRODUCTION

Hepatitis C virus infection is a serious worldwide problem. It has been estimated that there are 130–150 million HCV infection worldwide, with 350 000 to 500 000 people die each year from hepatitis C-related liver diseases [1].

Portal hypertension which is considered as one of the most important complications of liver cirrhosis is associated with development of a hyper dynamic circulation and complications such as ascites, hepatic encephalopathy and oesophago-gastric varices. Patients with cirrhosis and gastro-oesophageal varices have a hepatic venous pressure

gradient during hemodynamic catheterization of at least 10-12 mmHg [2].

Estimated prevalence of esophageal varices is approximately 50%. The risk of bleeding from varices is 25%-35% with majority of the initial bleeding occurring within 1 year from varices detection [3].

Variceal bleeding is associated with a high morbidity and mortality The mortality associated with each episode of variceal bleeding ranges from 17% to 57% [4].

The incidence of bleeding can be reduced with nonselective beta-blockers [5].

It is also suggested that prophylactic endoscopic variceal band ligation can decrease the incidence of variceal bleeding and mortality in patients with liver cirrhosis who have large varices [6].

The prevalence of oesophageal varices among cirrhotic patients is variable, ranging from 24% to 80%. Therefore, endoscopic screening of all patients with liver cirrhosis would result in a large number of unnecessary additional burden to endoscopic units [7].

Several studies have examined how to identify patients with varices using non-invasive or minimally invasive methods to avoid endoscopy in patients with a low risk of varices. These studies include biochemical, clinical and ultrasound parameters, transient elastography, CT scanning and video capsule endoscopy [8].

Insulin resistance (IR) is exceedingly common in patients with hepatitis C virus (HCV)-related chronic liver disease [9].

IR has been systematically associated with advanced fibrosis and fibrosis progression in several reports [10].

Camma and his colleagues identify a high HOMA-IR score as a new independent predictor of the presence of esophageal varices [11].

## PATIENTS AND METHODS

**Study design:** Cross-sectional study.

### Patients

We enrolled in the study 50 newly diagnosed patients with Child A HCV cirrhosis, consecutively observed at Hepatology department at Shebein El Kom Teaching Hospital in the period between May to December 2014, fulfilling all criteria detailed below.

### Inclusion criteria:

Patients were included if they had a diagnosis of HCV cirrhosis based on liver biopsy.

### Exclusion criteria :

- (1) Advanced cirrhosis (Child-Pugh classes B and C).
- (2) Other causes of liver disease.
- (3) Human immunodeficiency virus infection.

(4) Current or previous history of ascites or hepatic encephalopathy or portal hypertensive bleeding.

(5) Hepatocellular carcinoma.

(6) Portal vein thrombosis.

(7) Current treatment with any dosage of insulin.

(8) Previous or current treatment beta-blockers, diuretics, or other vasoactive drugs.

(9) Parenteral drug addiction or alcohol abuse in the last year.

(10) Type 2 diabetes.

The study was performed after written informed consent from all patients.

### Clinical and Laboratory Assessment

The following data were collected at the time of recruitment: age, sex, weight, and height. Body mass index (BMI) was calculated as weight in kilograms/height in square meters. Patients with a BMI of 18.5 to 24.9 kg/m<sup>2</sup> were classified as normal, those with a BMI of 25 to 29.9 as overweight, those with a BMI of 30 or more as obese. Clinical examination for Signs of chronic liver disease.

A 12-hour overnight fasting blood sample was drawn at the time of recruitment to determine the serum levels of (AST-ALT-PT-INR-Urea-Creatinine-CBC-Albumin-Bilirubin-HCV RNA and blood glucose level) Serum insulin was determined by enzyme-linked immunosorbent assay (Monobid Inc. Lake forest, USA). IR was determined by the homeostasis model assessment (HOMA) method by using the following equation: Insulin resistance (HOMA-IR= Fasting insulin (μU/mL)×fasting glucose (mg/dl)/405 [12]. Cut off value for diagnosis of IR was ≥1.775 according to the international diabetes federation (IDF) (left) and Adult Treatment Panel III (ATP III) in non-diabetic individuals.

### Instrumental Assessment

After an overnight fast, all patients underwent an ultrasound examination with single viewer operator in supine position to detect the presence of liver cirrhosis (irregular surface, Irregular liver margins, coarse texture, attenuated hepatic veins, Relative enlargement of caudate lobe, signs of portal hypertension (presence of abdominal collaterals or splenomegally), ascites, portal vein diameter, splenic vein diameter, the span of the right lobe in the mid clavicular line on oblique view and classified as shrunken (<11 cm), average (11-15 cm) or enlarged (>15 cm) and to exclude hepatic focal lesion.

### Upper gastrointestinal endoscopy

Was done by the same endoscopist after fasting for at least 6 hours in left lateral position with examining esophagus for varices occurrence, size and risk signs of bleeding (red wales&cherry red spots and duodenum till second part and stomach for gastropathy and fundal varices.

Esophageal varices was graded on the basis of their size classification and according to AASLD guidelines as follows: Grade 1: Small straight cords of varices confined to the lower third of esophagus. Grade 2: Enlarged and tortuous varices occupying less than one third of the lumen. Grade 3: Large coil shaped esophageal varices occupying more than one third of the lumen [13,14].

### Statistical analysis

Statistical presentation and analysis of the present study was conducted SPSS V.20. Data was expressed into two phases:

I- Descriptive 1- Mean value (X) and Standard Deviation [SD]: for quantitative data. 2- Frequency and percnatage for qualitative data.

II- Analytic by t-student test and Chi-square test. P value > 0.05 was considered statistically non significant P value  $\leq 0.05$  was considered statistically significant. P value  $\leq 0.001$  was considered statistically highly significant. Variables found to be associated with the dependent variable at univariate logistic regression at a probability threshold of less than 0.10 were entered into multivariate

logistic regression models. To avoid the effect of co linearity, HOMA-IR score, blood glucose levels and insulin levels as well as platelet count, spleen diameter, and platelet count/spleen diameter ratio, were not included in the same multivariate model.

## RESULTS

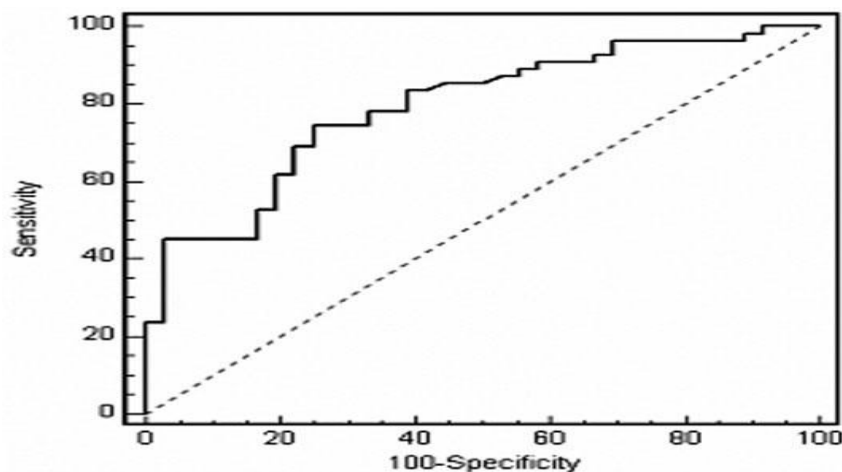
Study was conducted on 50 patients,30(60%) were males and 20(40%) were females. Mean age was  $42.32 \pm 10.13$ , mean BMI was  $33.8 \pm 2.73$  and mean HOMA-IR was  $31.43 \pm 3.23$ . Baseline features of studied cases are present in table (1).

In the present study varices was present in 18 (36%) of cases divided 11 patients was grade I and 7 patients was grade II. Factors associated with esophageal varices are shown in table (2).

In the present study high HOMA score and low platelets/splenic ratio were associated with varices presence. HOMA Cut off value was  $\geq 3.6$ , specificity 74%, sensitivity 67%, positive predictive value 77 and negative predictive value 63.

ROC curves analysis (Fig. 1) identified HOMA-IR score of  $\geq 3.6$  (AUC, 0.621; SE, 0.061; 95% CI, sensitivity, 67%; specificity, 74%; positive likelihood ratio, 2.82; negative likelihood ratio, 0.60) as the best cutoff for predicting the presence of EVs.

**Figure (1):** ROC curve for evaluating role of HOMA in prediction of varices



**Table (1):** Baseline features of studied cases (n=50)

Variable	Mean	Standard Deviation
Age (years)	42.32	± 10.13
BMI(body mass index) kg/m <sup>2</sup>	31.43	± 3.23
Waist circumference (cm)	107	± 3.1
Hemoglobin (gm/dl)	12.55	± 1.37
White blood cells (cell/mm <sup>3</sup> )	6582.0	± 2032.15
Platelet /mm <sup>3</sup>	135260	± 38644.19
Albumin (gm/dl)	4.0040	± 0.451
Total Bilirubin (mg/dl)	0.78	± 0.284
Direct Bilirubin (mg/dl)	0.24	± 0.222
Prothrombin time (seconds)	11.81	± 1.320
INR	.997	± 0.183
ALT (IU/L)	86.78	± 14.152
AST (IU/L)	101.68	± 16.531
Spleen Diameter (mm)	131.96	± 15.359
Splenic Vein (mm)	9.31	± 0.946
Platelet/splenic Index	1059.77	± 418.707
Urea (mg/dl)	31.28	± 6.259
Creatinine (mg/dl)	0.82	± 0.217
Fasting Sugar (mg/dl)	94.92	± 16.457
Fasting Insulin (µU/ml)	13.95	± 4.421
HOMA-IR	3.45	±1.39
Right liver lobe diameter (cm)	13.37	± 1.597
Portal vein diameter (mm)	13.25	± 2.460
<b>Child-Pugh</b>		
A5 45 (90%)    A6 5 (10%)		
<b>Esophageal varices</b>		
Present 18 (36%)		
Absent 32 (64%)		

**Table (2):** Correlation between Data of the study and esophageal varices by univariate and multivariate analysis

Variable	With varices n=18	Without varices n=32	Univariate Analysis P Value	Multivariate Analysis OR (95% CI) P Value
Age (years)	41.0 ± 9.35	43.06 ± 10.63	0.496	-
BMI(body mass index) kg/m <sup>2</sup>	33.8 ± 2.73	30.11 ± 2.72	0.002	0.624 (0.015)
Hemoglobin (gm/dl)	11.52 ± 1.01	13.14 ± 1.21	0.001	2.931 (0.024)
White blood cells (cell/mm <sup>3</sup> )	5727.77 ± 1772.94	7062.5 ± 2035.13	0.024	1.003 (0.987)
Platelet×10 <sup>3</sup> (cell/mm <sup>3</sup> )	71.0 ± 16.28	164.94 ± 23.1	0.001	-
Albumin (gm/dl)	3.59 ± 0.255	4.23 ± 0.366	0.001	1.405 (0.012)
Total Bilirubin (mg/dl)	0.989 ± 0.291	0.663 ± 0.204	0.001	0.005 (0.061)
Direct Bilirubin (mg/dl)	0.407 ± 0.201	0.148± 0.033	0.001	0.015 (0.066)
Prothrombin time (seconds)	12.88 ± 1.27	11.20 ± 0.906	0.001	0.251 (0.071)
INR	1.15 ± 0.185	0.909 ± 0.112	0.001	0.00 (0.091)
ALT (IU/L)	98.77 ± 10.07	80.03 ± 11.42	0.001	0.855 (0.001)
AST (IU/L)	117.33 ± 11.63	92.87 ± 11.64	0.001	0.817 (0.001)
Spleen Diameter (mm)	147.22 ± 14.84	123.37 ± 6.39	0.001	-
Splenic Vein (mm)	10.25 ± 0.289	8.78 ± 0.755	0.001	0.00 (0.989)
Platelets/splenic Index	562.75 ± 99.16	1339.35 ± 218.17	0.001	0.855 (0.001)
Urea (mg/dl)	29.83 ± 6.62	32.09 ± 6.0	0.224	-
Creatinine (mg/dl)	0.783 ± 0.217	0.853 ± 0.217	0.281	-
Fasting Sugar (mg/dl)	114.61 ± 8.49	83.84 ± 6.06	0.001	-
Fasting Insulin (µU/ml)	19.33 ± 1.51	10.93 ± 1.85	0.001	-
HOMA-IR	5.49 ± 0.754	2.29 ± 0.518	0.001	1.0 (0.020)
Right liver lobe diameter (cm)	11.36 ± 0.564	14.51± 0.412	0.001	0.00 (0.996)
Portal vein diameter (mm)	16.25 ± 1.14	11.56± 0.830	0.001	0.00 (0.995)

## DISCUSSION

Portal hypertension is one of the main consequences of cirrhosis. It can result in severe complications, including bleeding of esophago-gastric varices as well as spontaneous bacterial peritonitis or hepatorenal syndrome (HRS) as complications of ascites [15].

American Association for the Study of Liver Diseases 2007 single-topic symposium on portal hypertension [2] have recommended endoscopic screening for EV in patients with cirrhosis, regardless of Child class and cause. This policy is expensive, and it would be useful to have noninvasive predictors of EV in compensated Child A patients, at low risk of portal hypertension, as a pre-endoscopy screening tool. This goal was reasonably attained in the current study.

Several studies in chronic liver diseases have shown a strong and independent pathogenic link between IR (insulin resistance) and HCV infection [10,16] and between IR and the severity of hepatic fibrosis [9,10,16]. Although our work was not designed to clarify the pathogenic interaction between IR and presence of EVs, a few hypotheses can be put forward. Insulin is able to modulate the endothelial synthesis of nitric oxide and endothelin [17,18], to induce the production of tumor necrosis factor alpha and connective growth factor, and to stimulate hepatic stellate cells, [19,20] the effectors in the pathogenesis of liver fibrosis and PH [21]. Therefore, insulin could contribute to the pathogenesis of PH by interfering with both mechanical and dynamic mechanisms leading to collagen deposition, vasoconstriction, and regulation of sinusoidal structure.

The study was conducted on 50 cirrhotic patients (Child A) post hepatitis C who attended the Hepatology department and outpatient clinic at Shebein El Kom Teaching Hospital.

In this study we aimed to identify HOMA-IR score, an easy biochemical marker, predicting the presence of EVs.

Several studies have shown that splenomegally [22,23], Child score [24], low serum HB level [24], low platelets [25,26], low albumin [27,28], liver enzymes [29], prothrombin time [24,28], high portal vein diameter [28], high splenic vein diameter [30], right liver lobe diameter [31] and Platelets count/spleen diameter ratio [11,32-35] could serve as predictors of EVs presence. However, all of these studies were quite

heterogeneous, enrolling patients with cirrhosis of different causes (viral, alcoholic, and mixed) and different disease severity (Child B or end stage liver disease).

In our study HOMA-IR score for measuring insulin resistance was found higher in patients with varices (mean=  $5.49 \pm 0.754$ ) than patients without varices (mean=  $2.29 \pm 0.518$ ) as patients with varices were obese with central type. Statistically there was significance between high HOMA-IR score and esophageal varices presence ( $p=0.001$ ). Cut off value was  $\geq 3.6$ , specificity 74%, sensitivity 67%, positive predictive value 77 and negative predictive value 63. As reported by Camm`a and his colleagues [11] that there was relation between HOMA-IR score and esophageal varices with cut off value  $>3.5$ , specificity 76%, sensitivity 61%.

The small number of patients included in our study and differences among studies in terms of demographic features, baseline severity, and cause of disease may explain the conflicting results, as well as differences in the statistical methods.

On performing multivariate logistic regression analysis, it was found that high body mass index, low hemoglobin level, low albumin level, high ALT, high AST, low PLT/Splenic ratio and high HOMA-IR score are significant predictors of esophageal varices presence.

The study has limitations. First, the analysis was carried out in a small number of patients, and it will be interesting to determine whether this association holds true also in larger groups of patients with HCV cirrhosis and in patients with liver disease of other origins. Lack of data on other variables, such as direct measurement of portal hypertension by HVPG, also could affect the interpretation of our findings. Finally, we cannot exclude the possibility that hidden abuse of alcohol may be responsible for the presence of EV in a few subjects.

In conclusion, insulin resistance in patients with Hepatitis C virus cirrhosis (Child A) measured by HOMA-IR score significantly predicts the presence esophageal varices in this patients and can be used as non-invasive parameter for predicting esophageal varices, and it is cheaper than endoscopy but not sufficient to be good negative test or surrogate marker alone, still endoscopy is the gold standard for diagnosis of varices.

## ACKNOWLEDGEMENT

The authors would thank Dr. Muhammed El Shewi and Dr. Sabry Abbas who helped in conducting this study.

**Funding:** None.

**Conflicts of interest:** The authors declare that there is no conflict of interest.

**Ethical approval:** Was granted by the Institutional Review Board and informed consent was obtained from each patient prior to inclusion in the study.

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