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Relation between Serum Homocysteine level and Esophageal Varices in Cirrhotic Patients

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Abstract

Background: Liver disease accounts for approximately two million deaths per year worldwide, one million due to complications of liver cirrhosis (LC). **Aim**: This study aims to assess relation between the level of serum Homocysteine and esophageal varices in cirrhotic patients and if can be used as a marker for predicting esophageal varices in cirrhotic patients. **Methods**: This prospective study was carried out on 90 patients with established liver cirrhosis based upon clinical, laboratory and ultrasonographic findings in Faculty of Medicine Kafr Elsheikh University. They were divided into 2 groups; Group (A) Included 45 cirrhotic patients with Esophageal varices based on GI endoscopy and Group (B): Included 45 cirrhotic patients without Esophageal varices. **Results**: The optimal cut-off value for homocysteine identified in this analysis was 23.483 µmol/L, achieving both high sensitivity and specificity (93.33% for each). This level of accuracy suggests that homocysteine is an excellent biomarker for identifying patients with and without esophageal varices. **Conclusion**: The study conclusively demonstrates that serum homocysteine levels are significantly elevated in cirrhotic patients with esophageal varices compared to those without, making it a reliable predictive marker for the presence of varices. **Keywords**: Homocysteine; Esophageal Varices; Cirrhotic Patients

Introduction

Liver disease accounts for approximately two million deaths per year worldwide, one million due to complications of liver cirrhosis (LC). According to the Global Burden of Disease 2010 study, LC is the 11th most common cause of death globally, and accounting for 1.6% of the worldwide burden **(1)**.

Esophageal varices are Porto-systemic collaterals i.e., vascular channels that link the portal venous and the systemic venous circulation. They form as a consequence of portal hypertension (a progressive complication of cirrhosis), preferentially in the sub mucosa of the lower esophagus **(2)**.

Homocysteine (Hcy), a metabolic by-product of methionine, is an essential amino acid derived from dietary protein **(3)**. High levels of Hcy or hyperhomocysteinemia (HHcy) increases the risk of heart and vascular diseases as well as other pathological conditions, such as encephalopathy, kidney disease, and liver disease **(4)**.

Serum homocysteine could serve as a convenient novel and reliable noninvasive early diagnostic marker for SBP in cirrhotic patients with ascites **(5)**.

Some recent studies have suggested that HHcy as a result of abnormal hepatic homocysteine metabolism due to chronic liver disease (CLD) plays an important role in the occurrence and development of hepatic encephalopathy by activating NMDA receptors **(6)**.

This study aims to assess relation between the level of serum Homocysteine and esophageal varices in cirrhotic patients and if can be used as a marker for predicting esophageal varices in cirrhotic patients.

Patients and Methods

This prospective study was carried out on 90 patients with established liver cirrhosis based upon clinical, laboratory and ultrasonographic findings in Faculty of Medicine Kafr Elsheikh University. They were divided into 2 groups: Group (A) Included 45 cirrhotic patients with esophageal varices based on GI endoscopy. Group (B): Included 45 cirrhotic patients without esophageal varices.

An informed written consent was obtained from the patients. Every patient received an explanation of the purpose of the study and had a secret code number.

Inclusion criteria: Over 18 year's old, Cirrhotic patients and both sexes

Exclusion criteria: Patients with hepatocellular carcinoma, patients with portal vein thrombosis, patients with heart failure, patients with renal impairment, patients with thyroid hypofunction and patients with spontaneous bacterial peritonitis.

Methods: All studied cases were subjected to the following:

Detailed history taking, including: Personal history: age, sex, residence, occupation, and special habits including smoking or alcohol consumption.

Full clinical examination: General examination including: Vital signs: pulse, blood pressure, capillary filling time, respiratory rate, and temperature. **Systemic examination including:** Cardiovascular System: For detection of any abnormality including abnormal heart sounds or murmurs. Abdominal examination: For assessment of hepatomegaly, ascites, splenomegaly, and signs of portal hypertension such as spider angiomas, caput medusae, and collateral venous circulation and also evaluating for any signs of hepatic encephalopathy or jaundice.

Routine laboratory investigations: Blood samples were drawn for: Complete blood count (Hemoglobin, White Blood Cells, Platelets), liver function tests ALT (U/L), AST (U/L), Serum Bilirubin total & direct (mg/dL), Serum Albumin (g/dL), viral markers; hepatitis C virus antibodies (HCV-Ab) and hepatitis B surface antigen (HBsAg), coagulation profile: Prothrombin Time (PT) and International Normalized Ratio (INR), serum alpha fetoprotein (AFP) (ng/mL), kidney function testes (Serum creatinine (mg/dL), Urea (mg/dL)), eGFR (ml/min) and CRP (mg/L)

Radiological evaluation: Pelvi-abdominal ultrasonography was done to assess liver size, echogenicity, nodularity, portal vein patency, and the presence of ascites, hepatic lesions, or signs of portal hypertension such as splenomegaly or collateral circulation. and to exclude HCC. A diagnosis of cirrhosis was made with ultrasound when the liver appeared to be small and was accompanied by a nodular liver surface and coarse liver parenchyma. Spleen size was calculated as the product of the oblique and diagonal diameters from spleen hilum and ≥ 20 cm^2 was defined as splenomegaly.

Esophagogastroduodenoscopy: EGD was done to identify high-risk Esophageal Varices (medium or large EV, or small EV with red wale marks). Patients were kept nothing per oral for 6 hours prior to the procedure.

Child Pugh score: Prothrombin time (PT), serum albumin, total serum bilirubin, presence and degree of ascites and encephalopathy were assessed and the Child-Pugh score was calculated.

Collection, processing, and analysis of blood samples: With all aseptic precaution 2 ml venous blood (fasting) from the median cubital vein of each study subject was collected in a red test tube following standard procedure. After collection, tubes were labeled with the patient's identification number and kept in vertical position for 30 minutes. Then blood was centrifuged at 3000 rpm/minutes for 5 minutes in room temperature (22˚C - 24˚C). Serum was separated by micro-pipette and collected into appendrope, then preserved at −20˚C temperature until further analysis. Collected every test sample was run two successive days per week. Serum homocysteine level was estimated by automated immunoassay analyzer with the principle of chemiluminescent microparticle immunoassay (CMIA).

Ethical considerations: An approval from the Research Ethics Committee of Kafr El-Sheikh faculty of medicine was obtained. An informed written consent from all patients or first-degree relatives before participation was obtained; it included data about aim of the work, study design, site, time, subject and methods, confidentiality. Official permission was obtained from the Dean of Kafr El-Sheikh Faculty of Medicine and the administrators of Kafr El-Sheikh University Hospitals to conduct this study.

Statistical Analysis: The collected data was revised, coded, and tabulated using the Statistical package for Social Science (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). Data were presented and suitable analysis was done according to the type of data obtained for each parameter.

Results

The current study was carried on 90 patients with established liver cirrhosis based upon clinical, laboratory and ultrasonographic findings.

They were divided into 2 groups: Group (A) Included 45 cirrhotic patients with esophageal varices based on GI endoscopy. Group (B): Included 45 cirrhotic patients without esophageal varices

Table 1: Comparison between study groups according to demographic data

		Group A	Group B	Test Result
		n=45	n=45	
Age (years)	Mean ± SD	55.13 ± 3.76	53.84 ± 3.35	t: 1.646, p=0.099
	Median (Min-Max)	56.00 (49.00-60.00)	53.00 (49.00-60.00)	
Gender	Female	10(22.2%)	9(20.0%)	X2: 0.000, p=1.000
	Male	35(77.8%)	36(80.0%)	

t: independent t student test, X2: Chi square test

The demographic comparison between Group A and Group B reveals no significant differences in age (p=0.099) or gender distribution (p=1.000), indicating that the study groups are well matched in terms of basic demographic characteristics.

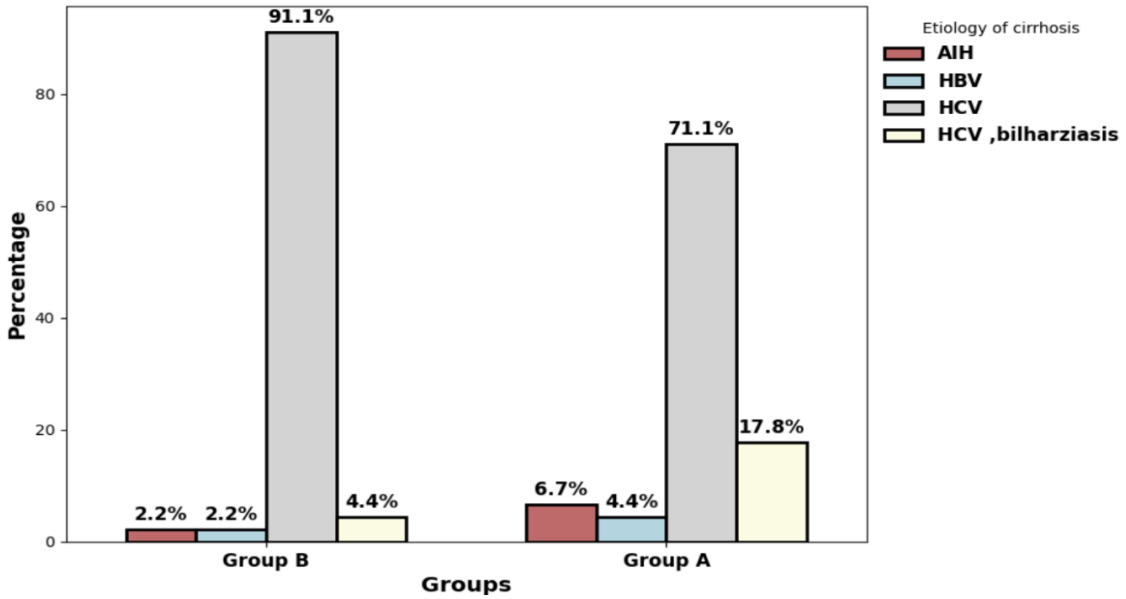

Figure 1: Comparison between study groups according to etiology of cirrhosis

Table 2: Comparison between study groups according to child pugh score

		Group A	Group B	Test Result
		n=45	n=45	
Child Pugh score	Mean ± SD	8.00 ± 0.83	6.76 ± 0.57	Z: 7.299, p<0.001*
	Median (Min-Max)	8.00 (7.00-9.00)	7.00 (6.00-9.00)	

Z: Mann whitney test, * for significant p value (<0.05)

According to CPS, Group A demonstrates a higher mean Child- Pugh score of 8.00 ± 0.83 as opposed to Group B's mean score of 6.76 ± 0.57. This marked difference is statistically significant, with a p-value of less than 0.001.

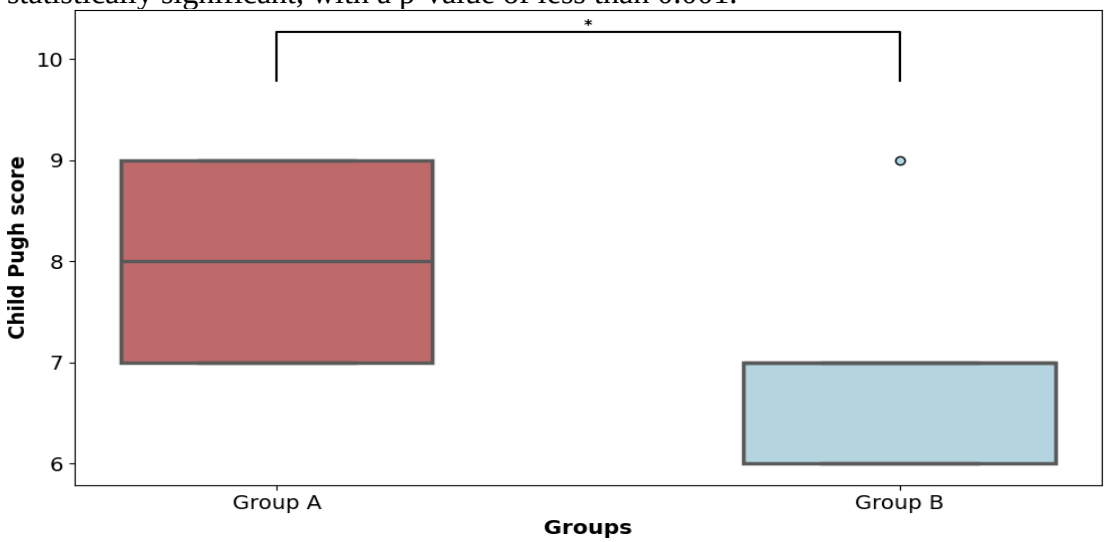

Figure 2.Comparison between study groups according to child pugh score

Table 3: Comparison between study groups according to homocystiene

		Group A	Group B	Test Result
		n=45	n=45	
Homocystiene (µmol /L)	Mean ± SD	20.38 ± 7.22	9.13 ± 3.05	Z: 7.594, p<0.001*
	Median (Min-Max)	19.09 (7.54-46.98)	9.38 (2.80-15.00)	

Z: Mann whitney test, * for significant p value (<0.05)

Regarding homocysteine levels, the mean homocysteine level in Group A is notably higher (20.38 ± 7.22 µmol/L) compared to Group B (9.13 ± 3.05 µmol/L), with the difference being statistically significant (p<0.001).

Table 4: Comparison between study groups according to EGD varices

	Category	Group A	Group B	Test Result
		n=45	n=45	
EGD varices	G1 Esophageal varices	13(28.9%)	0(0.0%)	X2: 90.000, p<0.001*
	G1,2 Esophageal varices	13(28.9%)	0(0.0%)	
	G2 Esophageal varices	8(17.8%)	0(0.0%)	
	G2,3 Esophageal varices	6(13.3%)	0(0.0%)	
	G3 Esophageal varices	3(6.7%)	0(0.0%)	
	G3,4 Esophageal varices	2(4.4%)	0(0.0%)	
	No varices	0(0.0%)	45(100.0%)	

X2: Chi square test, * for significant p value (<0.05)

According to endoscopic examination (EGD), the distribution of varices grades in Group A demonstrates different grades of esophageal varices ranging from G1 to G4 while in Group B all cases represented with no varices.

Table 5: Comparison between study groups according to associated EGD finding

Variable Name	Category	Group A	Group B	Test Result
		n=45	n=45	
Associated EGD finding	Antral gastritis	2(4.4%)	10(22.2%)	X2=5.333, p=0.021*
	Biliary reflux	1(2.2%)	0(0.0%)	X2=1, p=0.317
	Dudenal ulcer	0(0.0%)	2(4.4%)	X2=2.000, p=0.157
	GAVE	1(2.2%)	0(0.0%)	X2=1, p=0.317
	GERD	5(11.1%)	8(17.8%)	X2=0.692, p=0.405
	PHG	36(80.0%)	15(33.3%)	X2=8.647, p=0.003*
	No abnormal finding	0(0.0%)	10(22.2%)	X2=10.000, p=0.002*

X2: Chi square test, * for significant p value (<0.05)

Table 17 reveals significant differences in associated endoscopic findings between studied groups. Significant higher percentage of PHG in Group A compared to Group B (p=0.003). On the other hand a significant higher percentage of antral gastritis in Group B compared to Group A (p=0.021).

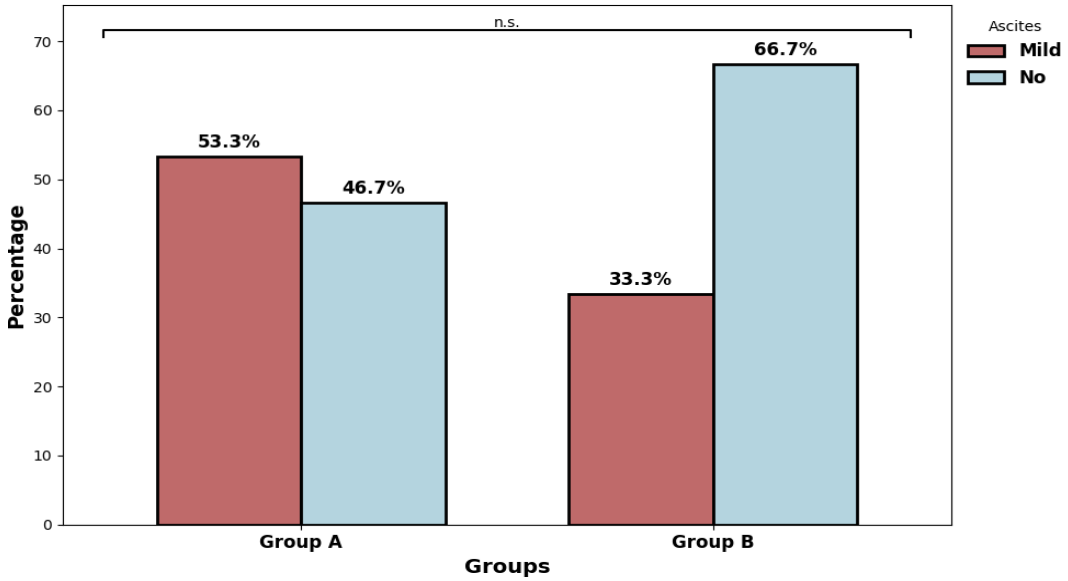

Figure 3: Comparison between study groups according to ascites

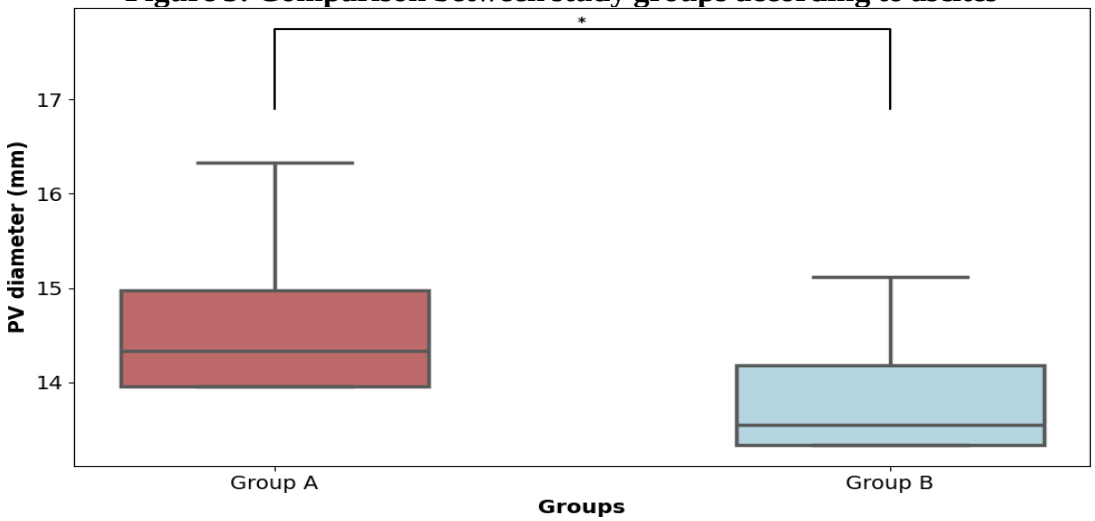

Figure 4: Comparison between study groups according to pv diameter

Table 6: Correlations between homocysteine and other studied parameters

Variable	rs	P-Value of
Age (years)	0.074	0.491
TLC (cells /µL)	-0.537	<0.001*
HB (g /dL)	-0.350	<0.001*
Platelet (10 3 /uL)	-0.737	<0.001*
AST (U /L)	0.662	<0.001*
ALT (U / L)	-0.695	<0.001*
ESR (mm /hr)	0.077	0.472
T. Bilirubin (mg /dL)	0.673	<0.001*
Albumin (g /dL)	-0.495	<0.001*
INR	0.701	<0.001*
Creatinine (mg /dl)	-0.112	0.293
AFP (ng /mL)	0.107	0.318
Child Pugh score	0.627	<0.001*
Spleen size (cm)	0.676	<0.001*
PV diameter (mm)	0.468	<0.001*

rs: Spearman correlation coefficient, * for significant p value (<0.05)

Correlation analysis presented in Table 21 demonstrates a notable interplay between homocysteine levels and a range of clinical and laboratory parameters in the studied patients. Significant negative correlations were noted between homocysteine with TLC, hemoglobin, platelets, and albumin. Conversely, strong positive correlations with AST, ALT, total bilirubin, INR, Child Pugh score, spleen size, and PV diameter. There were no significant correlation with age, ESR, creatinine, and AFP.

Table 7: Validity of homocysteine level in discrimination between different study groups

	AUC	95% CI	p	Cut off	Sensitivity (%)	Specificity (%)
Homocysteine	0.965	0.903 to 0.992	<0.001*	23.483	93.33	93.33

AUC, area under ROC curve; CI, confidence interval; *: Significant ≤0.05

Table 7 evaluates the diagnostic accuracy of homocysteine levels in discriminating between different study groups, utilizing the Area Under the Curve (AUC) from Receiver Operating Characteristic (ROC) analysis. The AUC for homocysteine is impressively high at 0.965 and a highly significant p-value of less than 0.001. The optimal cut-off value for homocysteine identified in this analysis was 23.483 µmol/L, achieving both high sensitivity and specificity (93.33% for each). This level of accuracy suggests that homocysteine is an excellent biomarker for identifying patients with and without esophageal varices.

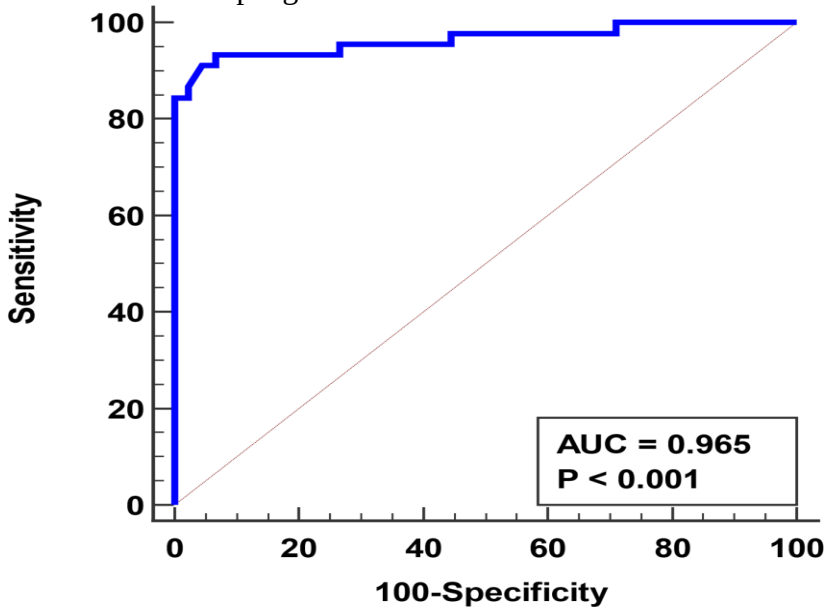

Figure 5: ROC curve of homocysteine in discrimination between different study groups

Table 8: Logistic regression analysis for prediction of esophageal varices among studied patients

	Univariate				Multivariate			
	p	Exp(B)	CI 5%	CI 95%	p	EXP(B)	CI 5%	CI 95%
Age	0.090	1.108	1.003	1.224	-	-	-	-
Gender	0.796	0.875	0.374	2.049	-	-	-	-

Etiology of cirrhosis (viral vs non viral)	0.330	0.318	0.046	2.197	-	-	-	-
Child Pugh score (B)	<0.001*	30.121	8.343	108.752	0.349	0.222	0.010	5.164
Homocystiene (high level)	<0.001*	2.018	1.554	2.621	<0.001*	0.471	0.314	0.707
Large PV diameter	<0.001*	10.114	4.266	23.981	0.04*	0.087	0.008	0.898

OR, odds ratio; CI, confidence interval., B, regression coefficient.,*:Significant ≤0.05

The results of logistic regression analyses conducted to identify predictors of esophageal varices among patients studied, comparing univariate and multivariate models. In the univariate analysis, significant predictors include the Child Pugh score, homocysteine levels, and large portal vein (PV) diameter, each associated with the outcome with p- values of less than 0.001, indicating strong statistical significance. In the multivariate analysis, only homocysteine and large PV diameter retain their significance, suggesting that when adjusting for other factors, these two variables independently predict the presence of esophageal varices.

Discussion

Liver disease represents a significant global health challenge, accounting for approximately two million deaths annually. Among these, cirrhosis—a condition characterized by the progressive scarring of liver tissue—stands out as a leading cause, contributing to one million deaths **(7)**.

The diagnosis of esophageal varices relies heavily on esophagogastroduodenoscopy, considered the gold standard in medical practice. This diagnostic method allows for the direct visualization and assessment of varices, facilitating timely and accurate identification of patients at risk of variceal bleeding **(8)**.

Therefore, this study aimed to assess relation between the level of serum Homocysteine and esophageal varices in cirrhotic patients and if can be used as a marker for predicting esophageal varices in cirrhotic patients.

This prospective study was conducted on 90 cirrhotic patients with established liver cirrhosis based upon clinical, laboratory and ultrasonographic findings in Faculty of Medicine Kafr Elsheikh University. Patients were divided into 2 groups: Group (A) Included 45 cirrhotic patients with esophageal varices based on GI endoscopy. Group (B): Included 45 cirrhotic patients without esophageal varices.

Regarding laboratory investigations, the analysis revealed a significant difference in TLC levels, with Group A showing a lower mean TLC (3.78 ± 0.58 cells/µL) compared to Group B (5.04 ± 1.42 cells/µL), as indicated by a highly significant p-value (<0.001). There was a statistically significant difference in hemoglobin concentrations, with Group A exhibiting lower average levels (10.19 ± 1.10 g/dL) than Group B (11.45 ± 1.15 g/dL), highlighted by a p-value of less than 0.001. Regarding platelet counts, Group A demonstrates considerably lower platelet counts (mean of 79.88 ± 5.52 x 10^3/uL) compared to Group B (mean of 105.65 ± 4.10 x 10^3/uL), with a highly significant p-value of less than 0.001.

The higher mean Child-Pugh score observed in Group A (patients with esophageal varices) compared to Group B (patients without esophageal varices) reflects a more advanced stage of liver cirrhosis in the former group. This difference, statistically significant with a p-value of less than 0.001, implies that the presence of esophageal varices is associated with more severe liver damage and functional impairment. The progression of liver cirrhosis to a point where portal hypertension prompts the formation of varices is marked by worsening liver function parameters included in the Child-Pugh score **(9)**.

In clinical terms, this association between higher Child-Pugh scores and the presence of esophageal varices highlights the necessity for vigilant monitoring and management of cirrhotic patients, particularly those with advanced liver disease, as indicated by their Child-Pugh classification. It emphasizes the importance of considering the presence of varices and their potential complications in the overall assessment and prognosis of liver cirrhosis. Furthermore, this correlation supports the use of the Child-Pugh score not only as a prognostic tool for liver disease but also as an indicator for the need for surveillance and possibly preventative treatment for esophageal varices, aiming to reduce the risk of variceal bleeding, a life-threatening event.

Regarding homocysteine levels, the mean homocysteine level in Group A is notably higher (20.38 ± 7.22 µmol/L) compared to Group B (9.13 ± 3.05 µmol/L), with the difference being statistically significant ($p<0.001$).

The finding that Homocysteine (Hcy) is higher in varices group can be attributed to that fact that it is considered that bacterial lipopolysaccharide endotoxins cause multiple-hour release of nitric oxide (NO) from vascular endothelium, what leads to peripheral vasodilatation, hypotension, and tachycardia. In vitro effect of endotoxin and cytokine on NO synthesis induction has been proved in endothelium and smooth muscles with progressive vascular relaxation and poorer response to vasoconstrictors. High circulating endotoxin concentrations were found in cirrhosis, which may persist even without evident clinical signs of infection.

Homocysteine and related biogenic thiols produce chemically and physiologically specific products in reactions with nitric oxides: nitrogen dioxide, dinitrogen trioxide and dinitrogen tetroxide. A tendency towards interaction with metal nitrosyl complexes is also manifested. In both cases, reaction products are S-nitrosothiol or thionitrites. These substances strongly activate the enzyme guanylate cyclase and are an important intermediary agent in metabolism of the endothelium-relaxing factor (EDRF). Elevated homocysteine levels in cells and extracellular space, by inducing the synthesis of vasoactive EDRF, are in-volved in the pathogenesis of hyperdynamic circulation.

Similarly, a study by **Culafić et al., (10)** was done to determine homocysteine values and factors affecting homo-cysteine metabolism in patients with liver cirrhosis. The prospective study included 35 patients with liver cirrhosis and 30 age and sex matched healthy controls. All the examinations were based on medical history, physical examination, laboratory tests including serum homocysteine levels and liver biopsy. The degree of liver failure was assessed according to the Child-Pugh classification. It was found that the mean plasma homocysteine levels were much higher in the patients with the cirrhosis than in healthy controls. A statistically significant difference was found between homocysteine plasma values in patients with cirrhosis and healthy subjects (14.85 ± 5.40 versus 9.17 ± 1.99 mol/L, t-test, $p < 0.001$).

According to endoscopic examination (EGD), the distribution of varices grades in Group A demonstrates a different grade of esophageal varices ranging from G1 to G4 while in Group B all cases represented with no varices.

Esophageal varices develop as a consequence of increased portal pressure, a hallmark of advanced liver disease, particularly cirrhosis. The liver's scarred tissue impedes normal blood flow, leading to portal hypertension, which, in turn, forces blood into collateral pathways, including the esophageal veins, causing them to dilate and form varices.

Consistently, a study by **Sumon et al., (11)** was performed to assess relation of different grades of esophageal varices with Child-Pugh classes in cirrhosis of liver. A total 37 patients were included. Child-Pugh score and esophageal varices of each patient were noted. Child-Pugh classes were observed 3(8.2%) Class A, 17(45.9%) Class B and 17(45.9%) Class C and grades of esophageal varies were 13(35.1%) F1, 20(54.1%) F2 and 4(10.8%) F3 patients among total. A statistically significant positive relation was found that higher grade of esophageal varices was seen in the more advanced class of Child-Pugh classes with a p value 0.001.

Regarding associated endoscopic findings between studied groups, Significant higher percentage of PHG in Group A compared to Group B (p=0.003). On the other hand, a significant higher percentage of antral gastritis in Group B compared to Group A (p=0.021).

On the other hand, the higher occurrence of antral gastritis in Group B, where portal hypertension may be less severe, suggests that other factors, possibly including Helicobacter pylori infection or non- specific inflammatory changes, might be more prevalent in the absence of significant portal hypertension. The statistical significance of these findings (p=0.003 for PHG and p=0.021 for antral gastritis) not only emphasizes the impact of portal hypertension on gastrointestinal pathology in cirrhosis but also suggests that the presence and type of gastric mucosal changes could reflect the underlying severity and progression of portal hypertension, offering insights into the comprehensive management of cirrhosis **(12)**.

Ascites was observed as mild in a higher proportion of patients in Group A (53.3%) compared to Group B (33.3%). However, the absence of ascites is more common in Group B (66.7%) compared to Group A (46.7%).

In correlation analysis, there were a notable interplay between homocysteine levels and a range of clinical and laboratory parameters in the studied patients. A significant negative correlation was noted between homocysteine with TLC, hemoglobin, platelets, and albumin. Conversely, strong positive correlations with AST, ALT, total bilirubin, INR, Child Pugh score, spleen size, and PV diameter. There was no significant correlation with age, ESR, creatinine, and AFP.

These findings suggest that higher homocysteine levels are closely associated with more advanced liver dysfunction, portal hypertension, and their hematological and metabolic consequences, reflecting the broad impact of cirrhosis on the body. Conversely, the lack of significant correlation with age, erythrocyte sedimentation rate, creatinine, and alpha-fetoprotein indicate that homocysteine's relevance is specifically tied to the pathophysiological manifestations of cirrhosis rather than age-related changes, systemic inflammation, renal function, or liver cancer markers. This highlights homocysteine's potential as a biomarker for assessing the severity of liver cirrhosis and guiding the management of its complications **(13)**.

The determination of an optimal cut-off value of 23.483 µmol/L, which yields both high sensitivity and specificity (93.33% each), further highlights the precision with which homocysteine levels can predict the presence of esophageal varices.

This finding has profound clinical implications. Firstly, it suggests that serum homocysteine levels could be utilized as a non-invasive screening tool to identify cirrhotic patients at high risk of having esophageal varices, thus enabling earlier and potentially life-saving interventions. The high sensitivity and specificity indicate that this marker can reliably differentiate patients, minimizing both false positives and negatives

The logistic regression analysis conducted in our study reveals critical insights into the predictors of esophageal varices in cirrhotic patients, distinguishing between factors identified through univariate and multivariate models.

The implications of these findings are manifold. Firstly, the predictive value of homocysteine levels and portal vein diameter in the multivariate context emphasizes their potential role in non-invasively identifying patients at higher risk for esophageal varices, offering a pathway towards more personalized and precise medical interventions. Clinically, this could guide decision-making regarding the need for prophylactic treatment or more frequent surveillance endoscopies, ultimately aiming to prevent variceal bleeding, a major complication of cirrhosis.

The significance of portal vein diameter as an independent predictor reflects its direct association with portal hypertension, a key driver in the formation of esophageal varices. This physical parameter encapsulates the culmination of various pathophysiological processes, including increased blood flow and vascular resistance within the portal system **(14)**.

Conclusions

The study conclusively demonstrates that serum homocysteine levels are significantly elevated in cirrhotic patients with esophageal varices compared to those without, making it a reliable predictive marker for the presence of varices.

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