DISCUSSION

Liver Cirrhosis is defined as a diffuse hepatic process characterized by fibrosis and conversion of normal liver architecture into structurally abnormal nodules leading to loss of liver function. Portal hypertension is the hemodynamic abnormality which develops in patients with liver cirrhosis. It results from increased splanchnic blood flow secondary to vasodilation within the splanchnic vascular bed as well as increased resistance to the passage of blood through the liver. [190] It is associated with the most severe complications of cirrhosis including ascites, hepatic encephalopathy and bleeding from gastro-esophageal varices.[191]

Gastro-esophageal variceal hemorrhage is a major complication of portal hypertension resulting from cirrhosis.[137] Variceal hemorrhage occurs in 25 to 35 percent of patients with cirrhosis and accounts for 80 to 90 percent of bleeding episodes in these patients.[120] Up to 30 percent of initial bleeding episodes are fatal and a higher percent of survivors have recurrent bleeding after the first variceal hemorrhage.[192] Therefore, early detection of esophageal varices and timely introduction of beta-blockers and band ligation for primary prevention of bleeding, decrease the morbidity and may improve quality of life in liver cirrhosis patients. For optimal management, it is important to understand which patients are most likely to have bleeding.

The present study was carried out on eighty subjects; sixty patients with liver cirrhosis and twenty control subjects. They were divided into four groups: Group I included twenty cirrhotic patients who were bleeders and have esophageal varices, group II included twenty cirrhotic patients who were non bleeders and have esophageal varices, group III included twenty cirrhotic patients who were neither bleeders nor have esophageal varices and group IV included twenty normal control subjects.

More than 90% of the patients included in the study were found positive for hepatitis C virus (HCV) antibodies, about 3% had hepatitis B virus surface antigen (HBs Ag) and about 3% had autoimmune hepatitis. This was in agreement with Khedr [193] who stated that Egypt has the highest HCV prevalence in the world and that chronic HCV is the main cause of liver cirrhosis in Egypt.

In our study, the age range of patients was between 25 and 71 years with no statistically significant difference among the studied groups. Males were the predominant gender representing 71% of all studied patients with no statistically significant difference among the studied groups. In agreement with these findings, Darwish et al.,[194] Nafeh et al.[195] and Abdel-Aziz et al.[196] demonstrated a marked growth in HCV prevalence with age. Furthermore, Arafa et al. [197] and Luksamijarulkul et al.[198] found a higher prevalence of HCV among males compared to females.

Spider angioma is one of the common peripheral stigmata of the chronic parenchymal liver disease. It is formed of a central arteriole, radiating from which are numerous small vessels resembling a spider's legs. It is found in the vascular territory of the superior vena cava and very rarely below a line joining the nipples. The selective distribution of vascular spiders is not understood. Our results showed a statistically significant higher percentage of spider angiomata among cirrhotic patients with EV compared to those without EV, also it was higher in patient with history of bleeding EV

more than those without history of bleeding EV. Like us, Dib N et al.[199], Garcia Tsao et al.[141] and Pilette et al.[200] found that the presence of spider angiomata was independent risk factor for the presence of EV. In contrast, Cales et al.[201] and Zaman et al[202] found that spider angiomata were not associated with the occurrence of large esophageal varices (LEV).

Thrompocytopenia is reported to be one of the most common hematological findings in cirrhotics. Pathogenesis of thrombocytopenia includes productive, consumptive or distributional mechanisms.[203]It is commonly believed to be due to pooling and destruction of platelets in the spleen which may be mediated by platelet associated IgG, bone marrow suppression[204] and reduced levels of thrombopoeitin either due to impaired production or rapid degradation[205,206]. In our study about 88% of the patients had thrompocytopenia. There was a statistical significant difference between cirrhotic patients with and without EV, also there was a statistical significant difference between bleeding EV (group I) and non bleeding EV(group II). Similar to our study Thabut et al[207], Garcia- Tsao et al.[141], Thomopoulos et al[208] reported low platelet count to be an independent risk factor for the presence of varices. Chalasani et al[125] proved that a platelet count <88,000/ mm3 was an independent risk factor for the presence of large varices. In retrospective analysis of 143 patients with compensated cirrhosis, Schepis et al. [209] reported EV in 63 patients (44%) with platelet count of <100,000/ mm3 as a predictor of EV.

Regarding liver profile of patients included in the study, a significant lower serum albumin and higher serum bilirubin were found in cirrhotics with EV compared to those without EV. However, no statistically significant difference was found between cirrhotic patients with and without history of bleeding EV. On the other hand prothrombin activity was significantly lower not only in cirrhotics with EV than without EV but also in cirrhotic patients with history of bleeding EV than those without history of bleeding.

There was no statistically significant difference between cirrhotic patients with and without EV, or between cirrhotic patients with and without history of bleeding EV regarding neither serum AST level nor serum ALT level.

Low serum albumin is an indicator of deranged hepatic function and the degree of hepatic dysfunction likely affects the development of portal hypertension via humoral factors and thus the development of varices. A study by Taso et al [141] found that low albumin level was a risk factor for development of varices . Also, in agreement with our results; Zein et al,[210] found that low albumin level was associated with the presence of esophageal varices in cirrhotic patients. Moreover, Serwar et al,[211] showed that serum albumin less than 2.95 gm / dl was associated with the presence of varices in cirrhotic patients.

In another study, Barrera et al.[212] found that serum bilirubin was significantly higher in cirrhotic patients with high risk EV than in patients without HREV (2.3 ± 2.3 versus 2.1 ± 2.4, p = 0.003), prothrombin activity was found to be lower in patients with HREV than in patients without HREV (p = 0.039).

In a similar study by Fagundes et al.[213], prothrombin activity less than 60%, serum albumin level less than 3.5 g/dl, and serum bilirubin more than 1.2 mg/dl were proved to be good predictors for EV among cirrhotic patients in univariate analysis, while only

platelets count and serum albumin were found to be independent risk factors for EV in multivariate analysis.

In contrast with our results, Chalasani et al.[125] and Ng et al.[214] found that serum bilirubin level, and prothrombin activity were not associated with the presence of EV in cirrhotic patients in multivariate analysis. Also Cales et al.[201] found that neither serum bilirubin, albumin, ALT, AST levels, nor prothrombin activity were found to be associated with the occurrence of EV/LEV. Similarly, Gill et al [215] found that serum bilirubin was not a good predictor of EV in cirrhotic patients however, in the same study, they demonstrated that INR of 1.5 was a reliable markers for predicting EV in cirrhotic patients and that serum albumin level was significantly lower in patients with EV than in patients without.

Child -Turcotte-Pugh (CTP) score is one of the most commonly used grading systems for assessing clinical severity and prognosis of liver disease. [216]

In our study the CTP score was statistically significantly higher in cirrhotics with EV than those without EV, but no significant difference was found between cirrhotic patients with and without history of bleeding EV. These finding were in agreement with Zaman[202] et al. who demonstrated that cirrhotic patients in Child-Pugh classes B or C were almost 3 times as likely to have esophageal varices or large esophageal varices as compared to patients in Child-Pugh class A. Another study by Wang MT [217] et al concluded that rebleeding in cirrhotic patients was associated with more blood transfusions, Child-pugh grade B rather than grade A, higher total bilirubin and creatinine. Also, Cherian JV et al [218] concluded from their work that the presence and higher grades of varices can be predicted by a low platelet count, Child-Pugh class B/C and spleen diameter.

In contrast, In 2007, Burton et al. [219] published the validation of a model for predicting size and presence of varices based upon platelet count and Child- Pugh class. The first model aimed to detect large varices in Child-Pugh A patients with a platelet count <80 and had a sensitivity of 58%, specificity 79%, positive predictive value (PPV) 30%, and negative predictive value (NPV) 92%. The second model aimed to identifying any varices in Child B/C patients with a platelet count <90 and had a sensitivity of 60%, specificity of 59%, PPV 80%, and NPV 34%. However, the performance of these models did not reliably predict the presence of esophageal varices.

Also in multivariate analysis, there was no correlation between the presence of EV and CTP classification. These findings were also reported by other researchers. [220]

Abdominal ultrasound is the most widely used imaging modality for assessing liver cirrhosis. It is helpful for confirming the diagnosis of liver cirrhosis, portal hypertension and grading of ascites, and to measure the diameters of right lobe of the liver, spleen and portal vein. [221]

In our work, portal vein diameter was significantly higher in cirrhotics with EV than cirrhotics without EV but there was no statistically significant difference between patients with EV either bleeders or non bleeders.

This was in agreement with study done by Schepis et al [209] who found that portal vein diameter more than 13 mm was significantly associated with presence of esophageal

varices. Gill et al [215] also identified esophageal varices in 70 % of cirrhotic patients with portal vein diameter > 13mm also Abd El- Wahab et al [222] stated that portal vein diameter > 13 mm is highly suggestive of portal hypertension and tendency for bleeding. In the same context Tarzamni et al [223] found that PV diameter were statistically higher in cirrhotic patients with EV than in cirrhotic patients without EV "$P < 0.001$", and in cirrhotic patients with LEV than in cirrhotic patients without large EV "$P < 0.001$ & $P = 0.037$ respectively".

In our study, splenomegaly was detected clinically in 100% of patients at initial assessment and this was confirmed by ultrasonographic examination. As regards spleen size, our results showed that the mean value of spleen size was significantly higher in those with varices than in those without varices and in those bleeders more than non bleeders. This finding was similar to D'Amico et al. [224] and Djordjević et al. [225] who stated that splenomegaly is frequent in patients with liver cirrhosis. The possible relationship between splenomegaly and portal hypertension has also been investigated in patients with cirrhosis by Bolognesi et al. [226] who found that splenomegaly in the setting of cirrhosis is not only caused by portal congestion, but also due to tissue hyperplasia and fibrosis .In fact, The increase in spleen size leads to an increase in splenic blood flow, which -in turn- participates in portal hypertension by actively congesting the portal system. Furthermore, Thombolus et al, [208] found that the presence of esophageal varices is directly correlated with splenomegaly and that the latter was a factor for prediction of esophageal varices in cirrhotic patients. Also Fagundes et al.[213] conducted a study on 85 cirrhotic patients and followed them up for 8 years, concluded that splenomegaly could predict the presence of EV. These finding was in agreement with Chalasani et al [125] who found that the presence of splenomegaly on physical examination was a risk factor for the presence of large varices.

Regarding ascites, there was a statistically significante difference between cirrhotics with EV and those without EV, but there was no statistical significant difference between EV bleeders and non bleeders. Many authors agreed that the presence of ascites is correlated to presence of esophageal varices and increased risk of bleeding. Chang et al.[227] found that patients having at least two among ascites, splenomegaly, and alcoholism would have an increased risk of having large esophageal varices. Also, Barrera et al. [212] found that higher proportion of clinical ascites was observed in patients with high risk EV compared with no high risk EV patients.

However, Sarangapani et al.[228] and Limquiaco et al[229] found that presence of different degrees of ascites did not increase the risk of bleeding from EV in cirrhotic patients also Zaman et al.[202] found no statistically significant difference between cirrhotic patients with and without EV, or between patients with and without bleeding EV regarding the degree of ascites or the presence of splenomegaly in U/S.

To summarize, most of these previous variables might have a role in the degree of portal hypertension and its complications. However, not every variable per se should be considered an independent predictor of the presence of EV and their risk of bleeding.

According to Baveno IV consensus the current recommendation is that all patients, at the time of initial diagnosis of cirrhosis, should undergo screening for gastroesophageal varices by UGIE. [132]

In the present study all cirrhotic patients were examined by UGITE revealing that 40 patients had EV (group I and II). In group I (cirrhotics with EV and history of bleeding) 16 patient (80%) had F2 EV and 4 patients (20%) had F3 EV. Risk signs of bleeding were present in 100% of them. In group II (cirrhotic with EV but with no history of bleeding, 11 patient (55%) had F1 EV, 8 patients (40%) had F2 EV and 1(5%) patient had F3 EV. Risk signs of bleeding were present in only 20% of them.

There was a statistically significant difference between group I and II regarding variceal size and risk signs of bleeding. The grade of gastric varices, and degree of portal hypertensive gastropathy were not found to be statistically different between cirrhotic patients with and without history of bleeding EV.

In accordance with our study, Dagradi [(111)] reported that patients with large varices and red spots had a high risk for esophageal varix hemorrhage. Also in a retrospective study, Beppu et al. [(109)] reported that various endoscopic stigmata on esophageal varices (e.g., red wale markings, cherry-red spots, and hematocystic spots) were significantly associated with the risk for esophageal variceal hemorrhage.

According to North Italian Endoscopic Club (NIEC) index which depend on the combination of clinical and endoscopic parameters the risk of first bleeding could be predicted and the first year percentage probability of bleeding could be calculated. In the present study, patient was scored according to NIEC index; revealing that there was a statistically significant difference between group I and II, being higher in group I (bleeders) than group II (non bleeders).

In a study by Snady et al [(230)] the NIEC index was prospectively validated for estimating the probability of developing a first esophageal varix hemorrhage in cirrhotic patients with varices. They reported that only 3 factors were independent risk factors for development of first esophageal varix hemorrhage: Child-Pugh class, size of the varices, and presence of red wale markings.

Merkel et al. [(231)] revised the NIEC index after performance of a prospective study to predict first esophageal variceal hemorrhage. By regression analysis and modeling, they reported that the size of esophageal varices and the presence of red wale markings were much more important than the Child-Pugh class for prediction of first esophageal variceal hemorrhage.

D'Amico [(232)] et al. and Cale [(201)] et al found that the size of the varices may change as the liver disease progresses they concluded that endoscopic screening should be repeated to determine whether esophageal varices are larger, which –in turn- would trigger a change in medical or endoscopic management of the patient for prevention of first esophageal varix hemorrhage.

In the past years and with the increasing number of patients with chronic liver disease needed to be screened endoscopically for presence of varices the identification of non invasive predictors become essential. So, many attempts were made to identify a predicator which will provide relief in medical, social and economic cost. Among these predictors were Platelet /spleen ratio, Right lobe/ albumin ratio and Aspartate amino transferase -to- platelet ratio index (APRI).

The presence of low platelet count may result from causes other than portal hypertension, like bone marrow suppression [204], reduced levels of thrombopoeitin either due to impaired production or rapid degradation[205,206]. shortened mean lifetime of platelets and myelotoxic effects of hepatitis viruses. On the other hand, the presence of splenomegaly in cirrhotic patients is the result of vascular disturbances that are mainly related to portal hypertension .Taking these facts into consideration, Platelet /spleen ratio was used as a predicator of esophageal varices. [233]

It was studied first by Giannini et al.[234] in 2003, they reported that the platelet count/spleen diameter ratio to be the only independent variable associated with presence of EV on multivariate analysis and identified a cut-off value of 909, giving a PPV of 96% and NPV of 100%. That study run in parrellel with Sethar et al [235] who showed that there was a significant difference in the mean value of the ratio between those with esophageal varices and those who did not , therefore, this can be used as a good discriminating parameter.

Furthermore, Baig et al [236] and Abu El Makarem MA [237] et al found that platelet to spleen ratio has an excellent accuracy in the noninvasive assessment of EV in patients with compensated or decompensated liver cirrhosis.

In our study there was a statistically significant difference in platelet count/spleen diameter ratio between cirrhotics with EV and cirrhotic without EV but there was no significant difference between cirrhotic with history of bleeding and cirrhotics without history of bleeding.

According to Alempijevic et al[238,239] the right liver lobe diameter:albumin ratio is a non-invasive parameters that can provide accurate information for determining the presence of esophageal varices and their grading in patients with liver cirrhosis. It was first assessed in a single study of 94 cirrhotic patients, where it was proved to correlate with presence and size of esophageal varices ($r = 0.488$, $p < 0.01$; $r = 0.481$, $p < 0.01$, respectively.

In our work and regarding right lobe to albumin ratio there was a statistical significant difference between cirrhotics with EV and cirrhotic without EV but there was no significant difference between cirrhotic with history of bleeding and cirrhotics without history of bleeding.

Regarding APRI we found that there was a statistical significant difference between cirrhotics with EV who had significantly higher values than cirrhotic without EV, but there was no significant difference between cirrhotic with history of bleeding and cirrhotics without history of bleeding.

In comparison, Sanyal et al. [240] studied 1016 clinically stable cirrhotic patients and reported that low platelets count and elevated AST, correlated with the presence of EV. They also found that APRI values higher than 1.64 were correlated with the presence of EV.

In contrast, Sebastiani et al. [241] found that there was only a weak correlation between APRI and the presence of EV (APRI=1.4; sensitivity 54%; specificity: 69%). Also Stefanescu et al [242] found that APRI performed even worse, showing an AUROC of only

0.57 for EV and 0.6 for LEV even after using a higher cutoff value than the ones proposed in the literature.

These contradiction results may be because APRI indicate more severe hepatic parenchyma architectural distortion (represented by fibrosis and sinusoidal capillarization) and increased intrahepatic circulatory resistance, resulting in portal hypertension. For a full understanding of this relationship, it would be ideal to determine hepatic venous pressure gradient, which was not performed in most of the studies.

The aim of the present study was to identify a new marker –GA/HbA1c- for assessing severity of liver cirrhosis and as a non invasive marker for predilection of esophageal varices and their risk of bleeding.First we studied serum GA and HbA1c separately for 60 cirrhotic patients and from these values we take the ratio between both markers.

Regarding GA, we found a significantly higher value among cirrhotics with EV than cirrhotics without EV. Also, the values were significantly higher in cirrhotics compared to control group. However, there was no statistically significant difference between cirrhotics with and without history of bleeding.

Regarding HbA1c there was no statistically significant difference between cirrhotics with EV and cirrhotics without EV. Also, no statistically significant difference was found between cirrhotics with and without history of bleeding but there was a statistically significant difference between cirrhotics and control group.

Regarding GA to HbA1c ratio, the values were significantly higher in cirrhotics with EV than cirrhotics without EV. Also there was a statistically significant difference between cirrhotics and control group. However, there was no statistically significant difference between cirrhotics with and without history of bleeding.

The ratio showed a significant positive correlation with Child score among all patients. However, it showed no correlation with NIEC index.

The diagnostic performance of GA/HbA1c ratio was compared to that of endoscopy, considered the gold standard, in patients presenting with esophageal varices. The receiver operator characteristic (ROC) curve analysis generated a ratio cut off value (COV) of 6.35 that could discriminate esophageal varices cirrhotic patients from non variceal cirrhotic patients, with an area under the curve of 0.711 (p=0.008). The ratio COV of 6.35 gave a diagnostic specificity of 85% , a sensitivity of 60%, and predictive values (positive and negative) of 89% and 52% respectively, making this method a rather specific one capable of detecting esophageal varices in cirrhotic patients (85%), than estimating the degree of its severity among such patients (60%).

Only few studies investigated the value of GA to HbA1c ratio as a marker for predicting EV.

Y *Sakai* et al [(243)] conducted a study on 47 Child-Pugh class A cirrhotic patients in an attempt to prove the possible relationship between GA to HbA1c ratio and the bleeding risk of EV. The study excluded patients whose GA/HbA1c ratios could have been influenced by poorly controlled diabetes. Patients were categorized into three groups (23

patient as “no varices group”, 22 patient as “low-risk varices group” and 22 patient as “high-risk varices group”).

Similar to our results, they found that GA/HbA1c ratio was significantly higher in patients with varices than that in patients without varices (p <0.001).

In contrast to our findings, however, they found that GA/HbA1c ratio was significantly higher in patients in the “high-risk varices group”, suggesting that the GA/HbA1c ratio is associated with an increased risk of variceal hemorrhage.

The difference between these results and our work may be due to several causes. The first cause was the small sample size (only 47 patients) in *Sakai*’s study. The second cause was the patients selection CTP- class A liver cirrhosis only, although according to Zaman[(202)] et al the risk of development of esophageal varices is three times more in child classes B and C than child A. This narrowed the scope of patient selection. Also, they only excluded patients with poorly controlled DM. In our work we study patients with all Child classes so we had more chance to select different patient varieties. Also we totally exclude patients with DM to avoid any bias in the result of GA/HbA1c ratio.

Again only few studies were done to investigate the relation of GA /HbA1c ratio with progression of liver fibrosis and liver disease severity.

Also in accordance with our results Bando et al.[(183)] reported that the GA/HbA1c ratio in patients with chronic liver disease has an inverse correlation with some indicators of hepatic function, regardless of the mean plasma glucose level, suggesting that the increase in the GA/HbA1c ratio reflects the reduction of liver function caused by the progression of liver cirrhosis.

Aizawa [(244)] et al studied the relation of the glycated albumin to glycated hemoglobin ratio during the progression of hepatitis C virus related liver fibrosis The study retrospectively included consecutive hepatitis C virus positive chronic liver disease patients (n = 142) who had undergone percutaneous liver biopsy between January 2008 and March 2010. The ratios of GA/HbA1c were calculated in all patients to investigate the relationship with the degree of the liver fibrosis. The GA/HbA1c ratio increased in line with the histological severity of liver fibrosis, thus suggesting that this ratio is useful as a supportive index of liver fibrosis. Its sensitivity for the detection of liver cirrhosis was 16/27 (59.3%) and the specificity was 81/115 (70.4%).

Enomoto et al [(245)] studied 176 HBV-positive patients to investigate the relationship between the ratios of glycated albumin-to-glycated hemoglobin (GA/HbA1c) in order to investigate the relationship with the degree of liver fibrosis. They found that the GA/HbA1c ratio increased in association with the severity of fibrosis and it was positively correlated with two well-known markers of liver fibrosis, FIB-4 ($P < 0.0001$) and AST-to-platelet ratio index (APRI) ($P < 0.0001$); however, the differences among the fibrosis stages were relatively small. Therefore, they concluded that GA/HbA1c ratio alone is not an ideal biomarker to evaluate liver fibrosis.

Bando et al [(246)] studied 36 patients with histologically diagnosed as NASH (19 men, 17 women; mean age 54.8±12.2 years, body mass index 28.3±5.0 kg/m2). The relationships of the GA/HbA1c ratio to hepatic function tests and fibrosis stage in the liver

were investigated and they found that the GA/HbA1c ratio in patients with NASH was inversely correlated with ALT ($P<0.001$) and platelet count ($P<0.0001$). Furthermore, the GA/HbA1c ratio was positively correlated with the fibrosis stage of the liver ($P=0.003$).

Finally, to summarize, our results indicate that the GA to HbA1c ratio might be a promising marker for the severity of liver cirrhosis. This – in turn- has its expected impact on the severity of portal hypertension and hence the formation of EV. However, the relation of GA to HbA1c ratio to the risk of bleeding was not proved in our work. Further studies with higher patient number will be needed in the future to clarify point of controversy.

SUMMARY

Liver cirrhosis is a chronic irreversible liver disease. Portal hypertension is a frequent complication of liver cirrhosis. Esophageal varices (EV) are frequently seen in patients with liver cirrhosis. Variceal bleeding is the most lethal complication of liver cirrhosis and portal hypertension.

Esophagogastroduodenoscopy (EGD) is considered to be necessary for all cirrhotic patients to evaluate the risk of variceal bleeding. Three factors identify patients at a high risk of bleeding from varices: large variceal size, red colour signs on the varices and advanced liver disease (Child-Pugh class B or C).

The increased flow of patients on endoscopy units might not meet demands of cost effectiveness for patients and hospitals.Some studies have evaluated possible non-invasive markers of esophageal varices in cirrhotic patients. The studies concluded that by selecting patients for endoscopic screening based on a few nonendoscopic variables, the number of unnecessary endoscopies will be reduced**.** The use of non endoscopic predictors of EV is interesting because they allow the selection of a subgroup of patients that are most likely to be favored by UGE.

Glycated proteins are known to reflect the plasma glucose level and glycated hemoglobin (HbA1c), is commonly used as an index of glycemic control in patients with diabetes mellitus. The HbA1c level is correlated with the level of glycemia for the past few months. Another glycated protein, glycated albumin (GA), reflects the plasma glucose level during the past few weeks.

Patients with chronic liver disease (CLD) have a shortened lifespan of erythrocytes, thus resulting in lower HbA1c levels relative to the plasma glucose level. Conversely, the turn-over period of serum albumin in CLD patients is increased to compensate for the reduced albumin production. Therefore, GA / HbA1c ratio was reported to be significantly increased in such CLD patients relative to the degree of glycaemia.

Furthermore, the GA / HbA1c in patients with CLD has been reported to show a reciprocal relation with some indicators of hepatic function, irrespective of the mean plasma glucose levels.

The aim of this work is to study serum GA to whole blood HbA1c ratio in liver cirrhosis in relation to severity of cirrhosis and risk of bleeding from esophageal varices. The study was carried out on 60 patients with liver cirrhosis and 20 healthy control subjects. They were divided into 4 groups:

- Group I: 20 patients with liver cirrhosis and EV which have previously bled.
- Group II: 20 patients with liver cirrhosis and EV which have not yet bled.
- Group III: 20 patients with liver cirrhosis without EV.
- Group IV: 20 normal healthy control subjects.

Any patient with malignancy, diabetes mellitus, endocrinal diseases, cardiovascular disease, pulmonary diseases, renal disease, collagenic diseases, on immunosuppressive therapy, also patient with EV band ligation, or sclerotherapy were excluded from this

study. None of them had had primary prophylactic treatment for variceal bleeding or any surgical treatment for portal hypertension.

The diagnosis of liver cirrhosis was based on clinical, biochemical, and ultrasonographic data.

All subjects were subjected to the following:

1) Detailed history taking.
2) Thorough clinical examination.
3) Laboratory investigations including: urine analysis, complete blood count, blood urea, serum creatinine, fasting blood glucose, serum alanine transaminase, serum aspartate transaminase, serum bilirubin, serum albumin, prothrombin activity, serum HCV antibodies, HBV surface antigen, autoimmune markers (antinuclear antibody (ANA), anti-smooth muscle antibody (SMA), liver/kidney microsomal antibody and anti-mitochondrial antibody (AMA) and complete urine analysis to exclude protienurea.

All patients were classified and scored according to modified Child-Pugh criteria.

4) Electrocardiogram and X-ray chest.
5) Calculation of the GA to HbA1c ratio after measuring serum HbA1c and Serum GA determination: using an enzyme immunoassay
6) Ultrasound abdomen
7) Upper gastrointestinal endoscopy was done for the cirrhotic patients using a video-endoscopy Olympus XQ 240.
8) IX calculation of different noninvasive ratios to assess EV:
   a) Platelet count spleen parameter ratio
   b) Right Lobe Liver Albumin ratio
   c) Aspartate amino transferase to platelet ratio index (APRI)

The results of this study showed the following:

1. More than 93% of patients included in the study were found to be positive for hepatitis C virus (HCV) antibodies and negative for hepatitis B virus surface antigen (HBs Ag).
2. There was no statistically significant difference between cirrhotic patients with and without EV, and between cirrhotic patients having EV with and without history of variceal bleeding regarding **age** and **gender**.
3. The number of patients with **jaundice, splenomegaly, hepatic encephalopathy, spider angioma and palmer erythema** were significantly higher in cirrhotic patients with EV than in cirrhotic patients without EV, but no statistically significant difference was found regarding these variables between cirrhotic patients with & without history of bleeding EV except for hepatic encephalopathy and spider angioma.

4. **Platelets** count was significantly lower in cirrhotic patients with EV than in cirrhotic patients without EV, and in cirrhotic patients with history of bleeding EV than in cirrhotic patients without history of bleeding EV. **Hemoglobin** was significantly lower in cirrhotic patients with EV than in cirrhotic patients without EV, but no statistically significant difference was found regarding it between cirrhotic patients with & without history of bleeding EV.

5. No statistically significant difference was found between cirrhotic patients with and without EV, or between cirrhotic patients with and without history of bleeding EV regarding **WBCs** count, blood **urea**, serum **creatinine**, **total protein** and **fasting blood glucose.**

6. Serum **bilirubin** level was significantly higher in cirrhotic patients with EV than in cirrhotic patients without EV, but no statistically significant difference was found regarding it between cirrhotic patients with & without history of bleeding EV.Serum **albumin** level was significantly lower in cirrhotic patients with EV than in cirrhotic patients without EV, but no statistically significant difference was found between cirrhotic patients with and without history of bleeding EV.

7. **Prothrombin activity** was significantly lower in cirrhotic patients with EV than in cirrhotic patients without EV, and in cirrhotic patients with history of bleeding EV than in cirrhotic patients without history of bleeding EV.

8. There was no statistically significant difference between cirrhotic patients with and without EV, or between cirrhotic patients with and without history of bleeding EV regarding serum **AST** level, serum **ALT** level, **GGT** level and **ALP** level.

9. **Child-Turcotte-Pugh** score was significantly higher in cirrhotic patients with EV than in cirrhotic patients without EV, but no statistically significant difference was found regarding it between cirrhotic patients with & without history of bleeding EV.

10. **Portal vein** diameter was significantly higher in cirrhotic patients with EV than in cirrhotic patients without EV, but no statistically significant difference was found regarding them between cirrhotic patients with & without history of bleeding EV.

11. **Spleen** diameter was significantly higher in cirrhotic patients with EV than in cirrhotic patients without EV, and in cirrhotic patients with history of bleeding EV than in cirrhotic patients without history of bleeding EV.

12. There was no statistically significant difference between cirrhotic patients with and without EV, or between cirrhotic patients with and without history of bleeding EV regarding longitudinal diameter of the **Right hepatic lobe.**

13. Degree of **ascites** was significantly more advanced in cirrhotic patients with EV than in cirrhotic patients without EV, but this was not found between cirrhotic patients with and without history of bleeding EV.

14. **Risk signs of bleeding**, **size of EV**, **NIEC** index and estimated risk of bleeding were significantly higher in cirrhotic patients with history of bleeding EV than in cirrhotic patients without history of bleeding EV.

15. Grade of **GV**, and degree of **PHG** showed no statistically significant difference between cirrhotic patients with and without history of bleeding EV.

16. **Platelet /spleen ratio, right lobe albumin ratio and Aspartate amino transferase -to- platelet ratio index (APRI)** were found to be more advanced in cirrhotic patients with EV than in cirrhotic patients without EV, but this was not found between cirrhotic patients with and without history of bleeding EV.

17. There was no statistically significant difference between cirrhotic patients with and without EV, or between cirrhotic patients with and without history of bleeding EV regarding **HbA1c** level.

18. **GA and GA/ HbA1c** ratio was significantly higher in cirrhotics more than control subjects and cirrhotic patients with EV than in cirrhotic patients without EV but this was not found between cirrhotic patients with and without history of bleeding EV.

19. There was a significant positive correlation between GA/HbA1c ratio and child score but there was no correlation between NIEC index and GA/HbA1c ratio.

20. The diagnostic performance of GA/HbA1c ratio was compared to that of endoscopy, the receiver operator characteristic (ROC) curve analysis generated a ratio cut off value (COV) of 6.35 that could discriminate esophageal varices cirrhotic patients from non variceal cirrhotic patients, with an area under the curve of 0.711 (p=0.008). The ratio COV of 6.35 gave a diagnostic specificity of 85% , a sensitivity of 60%, and predictive values (positive and negative) of 89% and 52% respectively, making this method a rather specific one capable of detecting esophageal varices in cirrhotic patients (85%), than estimating the degree of its severity among such patients (60%).

CONCLUSIONS

From this study we can conclude that

1) Platelet / spleen ratio, right lobe / albumin ratio and Aspartate amino transferase -to-platelet ratio index (APRI) continue to be a good markers for prediction of esophageal varices in patients with liver cirrhosis.

2) GA/HbA1c ratio is a new promising marker for predicting EV in cirrhotic patients. However, it does not correlate with the risk of variceal bleeding among these patients.

3) GA/HbA1c ratio correlate well with the severity of liver cirrhosis (expressed as Child score).

4) Glycated albumin level is higher in patients with cirrhosis compared to normal control subjects. it is also higher in cirrhotic patients with EV than those without.

5) Glycated hemoglobin level is lower in patients with cirrhosis compared to normal control subjects. However, it has no relation to the presence or absence of EV among cirrhotic patients.