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Prediction of Oesophageal Varices and Its Grades Using the Glycated Albumin to Glycated Haemoglobin (GA/HbA1c) Ratio in Egyptian Patients with Liver Cirrhosis

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Abstract:

Many non-invasive methods have been proposed to evaluate the presence and the grade of oesophageal varices (O.Vs). This work aimed to assess the value of GA/HbA1c ratio as a non-invasive predictor of OV and its grading. The study included 45 patients with established liver cirrhosis and oesophageal varices (subdivided into 3 groups according to the O.Vs grade), and 15 non cirrhotic patients as a control group. The history, clinical examination, laboratory investigations, ultrasound examination and Upper Gastrointestinal Endoscopy were done for all subject & GA/HbA1c ratio was calculated. There was a highly significant difference between patient and control, and between different patients' subgroups as regard the GA/HbA1c ratio and there was a high positive correlation between the GA/HbA1c ratio and grade of OVs in all patients' subgroups. These findings are suggestive that the increased GA/HbA1c ratio may be considered as a predictor for presence of O.Vs and its grade.

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Key words: Glycated albumin, HbA1c, non-invasive predictors, oesophageal varices.

INTRODUCTION:

According to the latest WHO data published in January 2015, Liver cirrhosis Deaths reached about 41.4 thousand patients representing the third leading cause of death in Egypt ***(WHO: Egypt Health profile, 2015).*** Portal hypertension is a major complication of liver cirrhosis and can be a direct cause of variceal haemorrhage and of bleeding-related deaths.

The upper gastrointestinal endoscopy (UGE) is still the gold standard method to diagnose early oesophageal varices and its bleeding and further complications ***(Garcia-Tsao et al., 2007).*** But endoscopy is costly, invasive technique and unpleasant procedure that some "patients at risk" would never agree to undergo UGE because of the perceived discomfort. In addition, it is unclear how often patients should be screened endoscopically for varices. Therefore, the importance of non-invasive predictors for early diagnosis of oesophageal varices has emerged.

Many studies in this field were done using platelet count, Insulin resistance, splenomegaly, bilirubinemia, PT, platelet count/spleen diameter ratio and serum fibrosis markers but their accuracy remains limited ***(Madhotra et al., 2002; Thomopoulos et al., 2003; Burton et al., 2007; De Franchis,2008; Eslam et al., 2013)***

Glycated hemoglobin (HbA1c) and glycated albumin (GA) are indexes of glycemic control in patients with diabetes mellitus. HbA1c depends on the lifespan of erythrocytes which is about 120 d. Glycated albumin correlates with the plasma glucose levels during the past few weeks because the turnover of albumin is about 20 d. Although the ratio of GA/HbA1c is usually close to 3, In patients with chronic liver disease (CLD),

hypersplenism shortens the lifespan of erythrocytes, leading to lower HbA1c levels relative to the plasma glucose level. On the other hand, the turnover periods of serum albumin in CLD patients is prolonged as a compensatory mechanism for the reduced production of albumin. Therefore, the GA levels in CLD patients are higher relative to the degree of glycaemia ***(Koga and Kasayama, 2010)***

Indeed, the GA/HbA1c ratio has been reported to be associated with the histological stage of liver fibrosis and portal hypertension in HCV-positive CLD and non-alcoholic steatohepatitis ***(Bando et al., 2009; Aizawa et al., 2012; Sakai et al., 2012; Bando et al., 2012)*** This study aimed to determine the relation between (GA/HbA1c) ratio and the oesophageal varices presence and its grading, in Egyptian patients with liver cirrhosis.

PATIENTS AND METHODS:

This case-control study included 45 patients with liver cirrhosis of any Child-Pugh grade attending the Gastroenterology-Hepatology department and endoscopy unit of internal medicine department at Ain Shams University Hospitals, and included 15 (non-cirrhotic) patients as a control group in the period from May 2014 to April 2015.

Subjects were divided into two groups:

Group I: included 45 patients with liver cirrhosis, diagnosed by the laboratory, endoscopic and ultrasonographic finings. This group was further subdivided into 3 subgroups according to the grade of the O.Vs and subsequently the risk of bleeding:

Group I A: 15 patients with grade I to II oesophageal varices, "low risk group".

Group I B: 15 patients with grade III to IV oesophageal varices, "medium risk group".

Group I C: 15 patients with oesophageal varices with red signs, "high risk group".
Group II: 15 non-cirrhotic patients (as control).

Exclusion criteria: Diabetic patients, renal impairment, previous history of upper GIT bleeding (Hematemesis & melena) or any previous intervention for the oesophageal varices, decrease RBCs life span like chronic haemolytic anaemia, recent blood donation in recent three months, cases of portal vein thrombosis and hepatocellular carcinoma.

All patients and controls were subjected to:

I. ***Full medical history taking and complete clinical examination:*** With special stress on previous history of chronic liver disease, symptoms of liver cell failure such as (jaundice, bleeding and encephalopathy) medical history of chronic disease as D.M. And examination of liver and spleen size, ascites & signs of liver cell failure as jaundice, palmar erythema and encephalopathy.

II. ***Laboratory investigations:*** including Complete blood count (CBC) and Erythrocyte sedimentation rate (ESR), Liver function tests (aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum albumin, total and direct bilirubin and Alkaline phosphatase), Prothrombin Time (PT in seconds), International Normalized Ratio (INR), Fasting Blood Sugar (FBS), two hours post prandial sugar, Renal function tests [Serum creatinine, Blood Urea Nitrogen (BUN), urea]

III. ***Glycated albumin to glycated haemoglobin ratio:*** Glycated albumin was measured by Sandwich ELISA technique utilizing a commercial kit manufactured by Glory Science. According to the manufacturer, the

assay range is 0.5 to 250 %. Glycated hemoglobin, however, was measured by an HPLC assay on Biorad automated system. The assay is linear up to a concentration of 10 %. Then the GA/HbA1c ratio was calculated.

IV. ***Abdominal ultrasound:*** To detect Portal Vein Diameter (PVD), liver span and spleen bipolar longitudinal diameter & ascites and to exclude other organomegaly, portal vein thrombosis or hepatocellular carcinoma**.**

V. ***Upper Gastrointestinal Endoscopy:*** Performed after written consent from patients under sedation to determine the grade of esophageal varices and the grade of Portal Hypertensive gastropathy:

- Grading of OVs was done according to Paquet grading system ***(Paquet., 1982):***

- Grade I: Microcapillaries located in distal oesophagus or oesophago-gastric junction.
- Grade II: One or two small varices located in the distal oesophagus.
- Grade III: Medium-sized varices of any number.
- Grade IV: Large-sized varices in any part of oesophagus.
    - **Red colour signs:** are red wale marks as longitudinal red streaks on varices, Cherry red spots, Hematocystic spots (raised discrete red spots overlying varices that resemble "blood blisters", Diffuse erythema denotes a diffuse red colour of the varix. ***(Bosch et al., 2003). (Kim et al., 1997)***

- Grading of Portal Hypertensive Gastropathy (PHG): was done according to Baveno grading system ***(De Franchis R, on behalf of the Baveno VI Faculty, 2015).***

- **Mild PHG:** Fine pink speckling (scarlatina-type rash), Superficial reddening Mosaic pattern.
- **Severe PHG:** Discrete red spots, Diffuse hemorrhagic brown lesion

VI. **Statistical analysis:** The collected data was revised, coded, tabulated and introduced to a PC using Statistical Package for Social Science (SPSS 15.0.1 for windows; SPSS Inc, Chicago, IL, 2001). Data were presented and suitable analysis was done according to the type of data obtained for each parameter.

Descriptive statistics

Mean, Standard deviation (± SD) and range for parametric numerical data, Frequency and percentage of non-numerical data.

Analytical statistics

Student t- Test was used to assess the statistical significance of the difference between two study group means. Analysis of variance (ANOVA) test is used to determine the statistically significant differences between the means of three or more independent (unrelated) groups. Correlation analysis: Pearson's correlation coefficient (r) test was used to assess the strength of association between two quantitative variables. The correlation coefficient defines the strength and direction of the linear relationship between two variables.

P- value (propability test): to assess the level of significance

$P>0.05$=Non-significant (NS).

$P\leq0.05$: Significant (S).

$P\leq0.01$: Highly significant (HS).

RESULTS:

This study was conducted on 45 patients with liver cirrhosis and oesophageal varices recruited from the Gastroenterology-Hepatology department and endoscopy unit of internal medicine department at Ain Shams University Hospitals in the period from May 2014 to April 2015.They were (24 male & 21 female), their age ranged from 40 to 65 years old and mean ± SD of 54.4 ± 5.79 years old. Fifteen non-cirrhotic patients of matching age and sex, attending the department for other complains were included as a control group.

Comparison between both patients and control groups: showed nearly a highly significant difference regarding different laboratory investigations **(table 1).** Also, comparing the two groups regarding the ultrasound findings, there was a highly significant difference as regards the splenic diameter and the portal vein diameter **(table 2).** Comparison between patients and control as regard Endoscopic results showed that the mean ± SD of the number of O.V cords was (3 ± 0.8), PHG was mild in 22 (48.9%) and severe in 17 (37.8%) of patients group.

Table (1): Comparison between patients and control as regard laboratory data.

	Patients	Control			
	Mean ± SD	Mean ± SD	**t-test**	p-value	Sig.
Hb (g/dL)	9.71 ± 0.60	10.83 ± 0.48	-6.474	<0.001	HS
Plt ($X10^3$/UL)	140.36 ± 53.98	377.27 ± 30.30	-16.114	<0.001	HS
AST (U/L)	53.93 ± 5.31	31.20 ± 7.86	12.656	<0.001	HS
ALT (U/L)	57.33 ± 6.46	30.40 ± 9.27	12.479	<0.001	HS
Alk.P (IU/L)	83.16 ± 26.40	64.93 ± 13.73	2.550	0.013	S
T.Bil (mg/dl)	1.15 ± 0.16	0.85 ± 0.09	6.548	<0.001	HS
D.Bil (mg/dl)	0.65 ± 0.09	0.45 ± 0.05	7.706	<0.001	HS
S.Alb (g/dl)	3.21 ± 0.48	4.43 ± 0.34	-9.032	<0.001	HS
PT (Sec)	17.89 ± 3.19	13.87 ± 1.06	4.769	<0.001	HS
INR	3.88 ± 16.64	1.02 ± 0.04	0.661	0.511	NS

Hb=haemoglobin, Plt=platelets, ALT=Alanine aminotransferase, AST=Aspartate aminotransferase, Alk.P=alkaline phosphatase, T.Bil=Total

Bilirubin, D.Bil =Direct Bilirubin, S.alb=serum albumin, PT=prothrombin time, INR=international normalized ratio.

Table (2): Comparisons between patients and control as regard Ultrasound examination.

	patients Mean ± SD	Control Mean ± SD	t-test	p-value	Sig.
Liver span (cm)	14.33 ± 2.74	13.33 ± 1.05	1.375	0.175	NS
Splenic diameter (cm)	17.58 ± 1.41	10.67± 1.40	16.512	<0.001	HS
PVD (mm)	16.5 ± 2.43	9.33 ±1.50	12.853	<0.001	HS
Ascites*	15 (33.34 %)	-	-	-	-

***is represented as the number (and %) of patients who had ascites.

Comparison between patient and control groups: there was a highly significant (HS) difference ($p<0.001$) as regard glycated albumin level (being higher in the patients group), comparing the glycated Hb levels showed a highly significant difference between both groups (being lower in the patients group), and by comparing the GA/HbA1c ratio there was a highly significant statistical difference between both groups being higher in the patients group (GA/HbA1c ratio =3.03±0.11 in the control group, and equals 4.3±0.57 in the patients group) **(table3).**

Table (3): Comparison between patients and control as regard Glycated Alb, Glycated Hb and the GA/HbA1c ratio:

	Patients (Mean ± SD)	Control (Mean ± SD)	t-test	p-value	Sig.
Glycated Alb (%)	15.86 ± 0.84	13.35 ± 0.42	11.006	<0.001	HS
Glycated Hb (%).	3.67 ± 0.34	4.37 ± 0.20	-7.601	<0.001	HS
GA/HbA1c Ratio	4.3 ± 0.57	3.03 ± 0.11	9.046	<0.001	HS

Comparison between the three patients' subgroups: regarding the laboratory investigations showed that there was a highly significant difference as regards (Hb, Platelet count, Alkaline phosphatase, total Bilirubin, serum Albumin and PT), also there was a significant difference by comparing AST, ALT and direct Bilirubin levels. And there was a highly significant difference between different patient subgroups by comparing

the liver span, splenic diameter and Portal vein diameter, and a significant difference as regard presence of ascites **(table 4).** There was a highly significant difference as regards grade of O.Vs and P.H.G **(table 5).**

Table (4): comparison between different cirrhotic patients' subgroups as regard laboratory data and U/S findings:

	Group Ia	Group Ib	Group Ic	ANOVA		
	(Mean ± SD)	(Mean ± SD)	(Mean ± SD)	F	P	Sig.
Hb (g/dl)	10.1 ± 0.49	9.79 ± 0.45	9.19 ± 0.45	16.348	<0.001	HS
Plt (X10³/UL)	196.87 ± 51.87	129.47 ± 22.52	94.73 ± 13.45	35.924	<0.001	HS
AST (U/L)	52.00 ± 4.87	52.87 ± 5.79	56.93 ± 4.06	4.233	0.021	S
ALT (U/L)	54.73 ± 5.43	55.40 ± 6.21	61.87 ± 5.46	7.138	0.002	S
Alk.P (IU/L)	64.07 ± 17.60	82.60 ± 30.50	102.80 ± 12.13	12.178	<0.001	HS
T.Bil (mg/dl)	1.03 ± 0.12	1.11 ± 0.14	1.30 ± 0.10	20.262	<0.001	HS
D.Bil. (mg/dl)	0.70± 0.08	0.61± 0.11	0.64 ± 0.07	3.724	0.032	S
S.Alb (g/dl)	3.70 ± 0.38	3.11 ± 0.35	2.83 ± 0.22	28.724	<0.001	HS
PT (sec)	14.93 ± 2.12	18.13 ± 1.77	20.60 ± 2.67	24.656	<0.001	HS
INR	1.19 ± 0.14	1.4 ± 0.18	1.57 ± 0.22	1.015	0.371	NS
Liver span (cm)	17.73±1.91	13.00±1.20	12.47±0.52	70.913	<0.001	HS
Splenic diameter(cm)	16.27±0.70	17.73±0.96	19.87±0.92	65.333	<0.001	HS
PVD (mm)	15.40±1.12	16.13±0.83	16.5±1.19	100.003	<0.001	HS
Ascites*	0 (0%)	6 (40%)	9 (60%)	5.904	0.015	S

Hb=haemoglobin, Plt=platelets, ALT=Alanine aminotransferase, AST=Aspartate aminotransferase, Alk.P=alkaline phosphatase, T.Bil=Total Bilirubin, D.Bil =Direct Bilirubin, S.alb=serum albumin, PT=prothrombin time, INR=international normalized ratio.

***is represented as the number (and %) of patients who had ascites.

Table (5): comparison between different cirrhotic patients' subgroups as regard Endoscopic findings:

Endoscopy:	Group Ia	Group Ib	Group Ic	ANOVA		
				F	P	Sig.
OV						
No of cords (mean±SD)	2.73 ± 0.88	2.93 ± 0.70	3.40 ± 0.63	3.142	0.053	NS
P.H.G						
Mild [No (%)]	10 (66.67%)	9 (60%)	2 (13.33%)	26.266	<0.001	HS
Severe [No (%)]	0 (0%)	5 (33.4%)	13 (86.67%)			

Comparing the glycated albumin values between the three patients' subgroups **(table 6)** showed a highly significant difference, being highest in group Ic "the high risk "group (mean ± SD is 16.64 ± 0.58 %). in contrast, the values of the glycated Hb (HbA1c) were of the lowest values in the high-risk group and there was a highly significant difference when comparing the three groups. The GA/HbA1c ratio was increasing with the increasing risk of bleeding, showing the lowest value in the "low risk" group (3.77 ± 0.24) and the highest value in the "high risk" group (5.03 ± 0.22)**.**

Tables (6): comparison between different patients subgroups as regard Glycated Alb, Glycated Hb and The GA/HbA1c ratio.

	Group Ia		Group Ib		Group Ic		ANOVA		
	Mean	± SD	Mean	±SD	Mean	±SD		p	Sig.
Glycated Alb (%)	14.97	±0.51	15.96	±0.37	16.64	±0.58	43.327	<0.001	HS
Glycated Hb (%).	3.99	±0.19	3.71	±0.16	3.31	±0.20	50.538	<0.001	HS
GA/HbA1c Ratio	3.77	±0.24	4.31	±0.22	5.03	±0.22	118.877	<0.001	HS

Correlating the GA/HbA1c ratio with other laboratory, U/S and endoscopic findings **(table 7)** showed that there was a significant positive correlation between the GA/HbA1c ratio and (the number of variceal cords and the PVD) in all subgroups. As expected, the ratio also correlated with the Hb and serum albumin levels. But non-significant correlation with (AST, ALT, Alk.P, total Bilirubin, direct bilirubin, liver span and splenic diameter). Platelet count was highly negatively correlated to

the AG/HBA1c ratio in the "High risk" group only. PT only correlated to the ratio in the low risk group.

Table (7): Correlation between the GA/HbA1c ratio and the Other Studied Parameters in the three patients' subgroups

All parameters	Group Ia		Group Ib		Group Ic	
	r	p-value	r	p-value	R	p-value
Age	0.434	0.106	0.035	0.901	0.277	0.318
Hb	-0.550	0.034*	-0.626	0.013*	-0.588	0.021*
Plt	-0.072	0.798	-0.097	0.732	-0.693	0.004*
AST	0.364	0.183	-0.175	0.532	0.362	0.184
ALT	0.352	0.199	0.114	0.685	0.466	0.080
ALK.P	0.463	0.083	0.347	0.205	0.208	0.457
T.Bil.	0.215	0.442	0.062	0.826	0.033	0.907
D.Bil	0.249	0.372	-0.038	0.892	-0.315	0.252
S.Alb	-0.532	0.041*	-0.315	0.253	-0.745	0.001*
PT	0.561	0.029*	0.357	0.191	0.485	0.067
INR	0.619	0.014*	-0.139	0.622	0.579	0.024*
Liver span	-0.164	0.559	-0.268	0.335	-0.249	0.370
Splenic diameter	-0.426	0.113	0.028	0.921	0.200	0.474
PVD (mm)	0.582	0.023*	-0.584	0.022*	0.652	0.008*
Endoscopy						
No of cords	0.871	<0.001**	0.379	0.032*	0.682	0.005*

Hb=haemoglobin, Plt=platelets, ALT=Alanine aminotransferase, AST=Aspartate aminotransferase, Alk.P=alkaline phosphatase, T.Bil=Total Bilirubin, D.Bil =Direct Bilirubin, S.alb=serum albumin, PT=prothrombin time, INR=international normalized ratio.

*significant difference, **highly significant difference.

DISCUSSION:

Non-invasive tests of liver fibrosis have revolutionized the management of chronic liver diseases. Compared with routine clinical assessments, the non-invasive tests allow more confident diagnosis of cirrhosis and can also reflect the severity of cirrhosis and/or portal hypertension. They can therefore be used to better select patients for varices screening and to allow cost saving by reducing the number of endoscopies.

The Transient Elastograghy combined with platelet count is the only recommended technique by The Baveno VI panel ***(DeFranchis, 2015)*** to diagnose portal hypertension.

However, researchers continue to look for an ideal (accurate, simple, inexpensive and easily reproducible) method.

A new biomarker based on a combination of metabolic parameters that includes the GA/HbAc ratio had been proposed as a useful tool for evaluating the risk of presence of oesophageal varices in patients with liver cirrhosis.

In this study, we aimed to assess the role of GA/HbA1c ratio as a screening test for the presence of oesophageal varices in Egyptian patients with liver cirrhosis. The second aim was to examine the possible correlation between the GA/HbA1c ratio and the grade of O.Vs.

We found that there was a highly significant difference between patients and control as regards the Glycated Albumin, HbA1c and the GA/HbA1c ratio. as compared by mean values, the GA/HbA1c ratio was (3.03) in controls and (4.37) in patients group, suggesting that the increased (GA/HbA1c) ratio may be considered as a predictor for presence of O.Vs. Furthermore, the GA/HbA1c ratio was significantly higher in patients in the "high risk varices group" as compared by mean value which was increasing from group Ia (3.77) to group Ib (4.31) to group Ic (5.03). There was a highly significant positive correlation between the GA/HbA1c ratio and the grade of Oesophageal varices suggesting that the increase of GA/HbA1c ratio is associated with a higher grade of O.Vs and subsequently with the risk of variceal bleeding and this was in agreement with (***Sakai et al., 2012)***.

Many previous studies (e.g. ***Madhotra et al. 2002; Wang et al., 2012; Eslam et al., 2013)*** have documented good predictive value of platelet count as a non-endoscopic variable for the presence or absence of varices. In our study, there was a highly significant difference between the three patients' subgroups as regards the platelet count. In addition, there was a highly significant negative correlation between the platelet count and the GA/HbA1c ratio in the "high risk" group.

Also, several studies have evaluated other blood tests to predict varices such as and AST-to-platelet Index ***(Tafarel et al., 2011; Colecchia et al., 2011; Morishita et al., 2014).*** Also, ***Park et al., 2009*** developed a simple risk score comprising bilirubin and platelets to predict Hepatic vein pressure Gradient (HVPG) and his results agreed with ***Procopet etal.,2015***. In the current study, there was a highly significant difference between different patients subgroups as regard liver function testes: (Platelet count, total Bilirubin, S. Albumin, PT) and also (Hb and Alkaline Phosphatase) were found to be better in group Ia (low risk) and worst in group Ic (high risk O.Vs) which suggested that there may be a relation between progression of chronic liver disease and the degree of O.Vs and this agrees with ***Tafarel et al (2011).*** Also there was a significant difference between different patients subgroups as regard (AST, ALT and direct Billirubin). (***Chang et al., 2007)*** agreed with our results that low serum albumin level and prolonged prothrombin time were significant with the presence of varices.

Many studies have adopted the ultrasound examination findings as predictors to diagnose portal hypertension. In our study, the PVD was highly significantly different in the three patients' subgroups. This goes in agreement with ***Hong et al., 2009; and Cherian et al., 2011*** who found that PVD was significant with the presence of O.Vs. In addition, we found that the GA/GHbA1c ratio was significantly correlated with the PVD in all patients' subgroups. ***Sharma and Aggarwal ,2007*** in a prospective study, observed that splenomegaly, increased liver span and platelet count were the independent predictors for the presence of large varices. In the current study, we also found highly significant differences between the three patients' subgroups regarding the liver span and the splenic bipolar diameter values.

In conclusion, we describe a predictive model for assessing the probability of the presence of O.Vs which can be used as an initial screening tool in cirrhotic patients. So far, the available data do not allow for the complete replacement of endoscopy in OV screening, but may help in confirming the necessity of endoscopy in those with suspected high risk of bleeding O.Vs. Our findings indicate that the GA/HbA1c ratio predicts the presence of oesophageal variceal and it can be considered in prognostic models in patients with cirrhosis and portal hypertension.

RECOMMENDATIONS:

Further prospective studies might be needed to find a cutoff value of GA/GHba1c ratio and this might result in a discriminating algorithm to predict which patients with cirrhosis would benefit from early or regular endoscopy to detect clinically significant varices. This cost effective parameter may help identify patients with mild or no O.Vs who may not need UGE to reduce costs and discomfort for these patients and the burden on health system.

CONFLICT OF INTEREST: The authors declare that there is no conflict of interests regarding the publication of this paper.

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