Evaluation of INR Elevation in Cirrhotic Patients as a Risk Factor for Esophageal Variceal Bleeding

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Background and study aim: Bleeding esophageal varices is a life threatening complication in cirrhotic patients. So, studying risk factors for bleeding esophageal varices is a must. Because of complexity and dynamic nature of coagulation process in cirrhotic patients, INR is considered a false method to measure bleeding risk in such patients. This study aims at evaluating INR elevation in cirrhotic patients as a risk factor for esophageal variceal bleeding.

Patients and Methods: This case control study was conducted at the Intensive Care Unit and inpatient wards of Tropical Medicine Department affiliated to Zagazig University Hospitals in the period from April 2016 to January 2017. According to inclusion and exclusion criteria, 202 patients with liver cirrhosis and esophageal varices were included in this study. Cases were cirrhotic patients admitted to the hospital due to first attack of actively bleeding esophageal varices. Controls were cirrhotic patients without bleeding esophageal varices admitted with ascites, SBP or hepatic encephalopathy.

Results: Median admission INR was 1.3 in bleeders compared to 1.9 in non-bleeders with a highly significant statistical difference between both groups.

Conclusion: Study concluded that INR elevation reflects the degree of liver dysfunction not the risk of bleeding from esophageal varices.

INTRODUCTION

Bleeding from esophageal varices in cirrhotic patients is considered a life threatening complication despite the improvement of medical and endoscopic lines of treatment with mortality ranging from 15 to 20 % **[1]**.

Correction of coagulopathy which is reflected by elevation of INR by fresh frozen plasma is a common clinical procedure during management of bleeding from esophageal varices. American Association for the Study of Liver Diseases (AASLD) recommends correction of coagulopathy and /or thrombocytopenia by transfusion of fresh frozen plasma and / or platelets in the setting of variceal bleeding **[2]**.

Because of complexity and dynamic nature of the coagulation process in cirrhotic patients, INR is considered a false method to measure bleeding risk in such patients **[3,4,5]**.

Severe hemorrhage from esophageal varices depends on portal hypertension more than function of the clotting cascade **[3]**. There are other risk factors of bleeding from varices such as alcohol use, large size and cherry red spots on varices. Size of varices and presence of cherry red spots reflect chronic increase of the intravariceal blood pressure **[6]**.

PATIENTS AND METHODS

This case control study was conducted at the intensive care unit and the inpatient ward of Tropical Medicine Department at Zagazig University Hospitals in the period from April 2016 to January 2017. Informed consents were obtained from all patients. Approval was obtained from the ethical committee of Faculty of Medicine affiliated to Zagazig University. There were no conflicts of interests nor funding during the study.

Patients with Child Pugh class B or C liver cirrhosis and bleeding or non-bleeding esophageal varices were included in the study. Diagnosis of liver cirrhosis was based on clinical, laboratory and imaging evidences and presence of esophageal varices was proved by upper endoscopy. Hemophiliacs, patients on warfarin treatment, those with TIPS and patients with uremia, heart failure or respiratory failure were execluded from the study.

According to inclusion and exclusion criteria, 202 patients with liver cirrhosis and esophageal varices were included and divided into 2 groups; group 1 (cases) included 101 cirrhotic patients with first attack of bleeding esophageal varices (admitted due to active upper GI bleeding) and group II (controls) included 101 cirrhotic patients without bleeding esophageal varices. Group II patients had esophageal varices proved by previous or current upper GI endoscopy and admitted for causes other than bleeding eg; ascites, SBP and hepatic encephalopathy.

All patients were subjected to full history taking, thorough clinical examination, routine laboratory investigations (CBC, LFT, PT, INR and KFT) and pelvi-abdominal ultrasound performed for all patients by the same operator. Child–Pugh score was determined for every patient accoding to Pugh modification of Child classification of liver cirrhosis **[7]**.

All patients were subjected to upper gastrointestinal endoscopy performed by the same endoscopist using endoflexible video endoscope (Pentax video unit of endoscopy).

Varices were graded according to the grading system suggested by Thakeb et al. **[8]** where grade I varices are small straight cords of varices confined to the lower 1/3 of the oesophagus, grade II varices are moderate sized clubbed varices with well-defined areas of normal mucosa in between forming several distinct vertical cords and confined to the lower 1/3 of esophagus, grade III varices are large tortuous varices extending into the proximal half of the esophagus with invisible mucosa in between unless the esophagus is fully distended with air and grade IV varices are varices like those of grade III but with risky signs (dilated capillaries on top, cherry red spots and varix over varix).

Portal hypertensive gastropathy (PHG) was graded according to the grading system suggested by Tanoue et al. **[9]** where grade 1 PHG is mild redness of the mucosa, grade 2 PHG is severe redness of the mucosa with fine reticular pattern in areas of raised mucosa and grade 3 PHG resembles grade 2 with point bleeding.

Obtained data were collected, tabulated and statistically analyzed using SPSS 22.0 for windows (SPSS Inc., Chicago, IL, USA) and MedCalc 13 for windows (MedCalc Software bvba, Ostend, Belgium). Continuous quantitative variables were expressed as the mean ± SD and median (range) and categorical qualitative variables were expressed as an absolute frequency (number) and a relative frequency (percentage). Continuous data were checked for normality using Shapiro Walk test. Independent samples Student's t-test was used to compare two groups of normally distributed data while Mann-Whitney U test was used for non-normally distributed data. Categorical data were compared using Chi-square test or Fisher's exact test when appropriate. All tests were two sided. P-value <0.05 was considered statistically significant (S), p-value <0.001 was considered statistically highly significant (HS) and p-value ≥0.05 was considered statistically non-significant (NS).

RESULTS

Table (1): Clinico-demographic data of both groups

		Bleeders	Non-Bleeders	Test	p	Sig.
Age, Years		54 ± 10	55 ± 8	-3.6*	0.06	NS
Sex	Female	31 (30.7%)	24 (23.8%)	1.2#	0.269	NS
	Male	70 (69.3%)	77 (76.2%)			
HE	No	99 (98.0%)	6 (5.9%)	171.5#	<0.001	HS
	Yes	2 (2.0%)	95 (94.1%)			
NSBB	Yes	42(41.58%)	29(28.71%)	3.7	0.055	NS
	No	59(58.42%)	72(71.29%)			

* Independent T test # Chi-square X^2 test HE: hepatic encephalopathy
NBBB: non selective beta blockers

Table (2): Sonographic data of both groups

		Bleeders	Non-Bleeders	$X^{2\#}$	p	Sig.
Liver	Enlarged	20(19.80%)	2(1.98%)	60.1	<0.001	HS
	Average	58(57.43%)	22(21.78%)			
	Shrunken	23(22.77%)	77(76.24%)			
HCC	Yes	18 (17.8%)	27 (26.7%)	$2.3^{\#}$	0.128	NS
	No	83 (82.2%)	74 (73.3%)			
PVD (mm)		16 ± 2	15 ± 1	-6.4*	<0.001	HS
PVT	Yes	12(11.88%)	19(18.81%)	1.9	0.172	NS
	No	89(88.12%)	82(81.19%)			
Spleen	Enlarged	98 (97.0%)	98 (97.0%)	$0.0^{\#}$	1	NS
	Removed	3 (3.0%)	3 (3.0%)			
Ascites	Non	22 (21.8%)	2 (2%)	$45.2^{\#}$	<0.001	HS
	Mild	46 (45.5%)	20 (19.8%)			
	Moderate	29 (28.7%)	67 (66.3%)			
	Massive	4 (4%)	12 (11.9%)			

* Independent T test # Chi-square X^2 test HCC: hepatocellular carcinoma
PVD: portal vein diameter PVT: portal vein thrombosis

Table (3): Laboratory data of both groups.

	Bleeders	Non-Bleeders	MWU*	p	Sig.
WBC ($x10^9$/ L)	5.6 (1.8-21)	6.1 (1.9-20)	-0.6	0.579	NS
Hb (gm / dL)	8.6 (5.3-12.4)	9.4 (7.3-13.2)	-3.6	<0.001	HS
Plt ($x10^9$ / L)	95 (27-365)	77 (21-201)	-1.6	0.117	NS
T. Bil (mg/dL)	2.1 (0.2-12.6)	4.4 (0.8-20)	-5.6	<0.001	HS
D. Bil (mg/dL)	1.3 (0.1-24)	2.8 (0.3-16)	-5.4	<0.001	HS
ALT (IU/L)	32 (8-143)	38 (11-211)	-2.4	0.017	S
AST (IU/L)	57 (14-280)	66 (19-303)	-2.9	0.004	S
INR	1.3 (1-1.9)	1.9 (1.3-3.4)	-10.2	<0.001	HS
PT (Sec)	15.7 (2.8-20.6)	23 (15-40)	-9.4	<0.001	HS
Alb (mg/dL)	2.7 (1.6-3.9)	2.3 (1.6-3)	-6.3	<0.001	HS
Cr (mg/dL)	0.9 (0.5-5)	1.3 (0.3-4.5)	-2.8	0.005	S

MWU* = Mann-Whitney U test

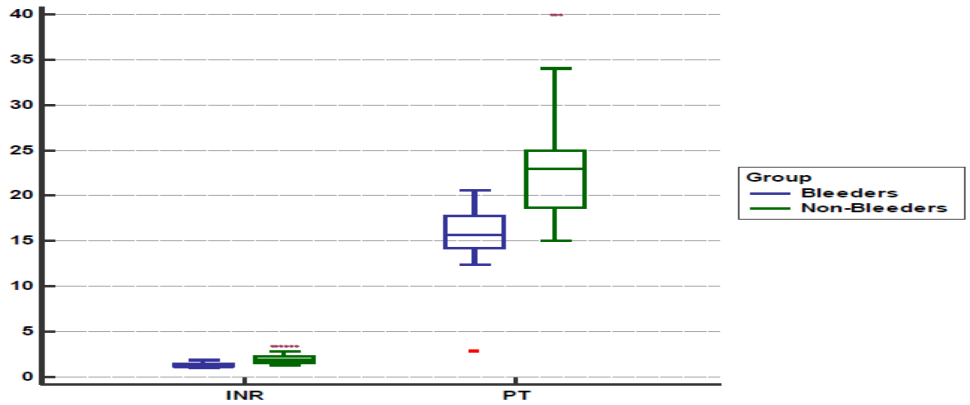

Figure (1): Box-plot diagram represents the range of INR and PT in the studied groups; the upper & lower line in each box represents the 75th and 25th percentiles respectively while the line through each box indicates the median.

Table (4): Child score of both groups.

		Bleeders	Non-bleeders Bleeders	Test	p	Sig.
Child	**B**	68 (67.3%)	4 (4.0%)	88.4#	<0.001	HS
	C	33 (32.7%)	97 (96.0%)			
Child Score		9 (7-11)	13 (8-15)	-11.3*	<0.001	HS

* Mann-Whitney Test # Chi-square X^2 test

Table (5): Endoscopic findings of both groups

		Bleeders	Non-Bleeders	$X^{2\#}$	p	Sig.
OV grade	G I-II	32 (31.7%)	90 (89.1%)	69.62	<0.001	HS
	G III-IV	69 (68.3%)	11 (10.9%)			
Risky OV	Yes	92 (91.1%)	76 (75.2%)	7.9	0.004	S
	No	9 (8.9%)	25 (24.8%)			
PHG	No	14(13.86%)	27(26.73%)	6.51	0.089	NS
	I	27(26.73%)	18(17.82%)			
	II	39(38.61%)	33(32.67%)			
	III	21(20.8%)	23(22.78%)			

Chi-square X^2 test OV: oesophageal varices PHG: portal hypertensive gastropathy.

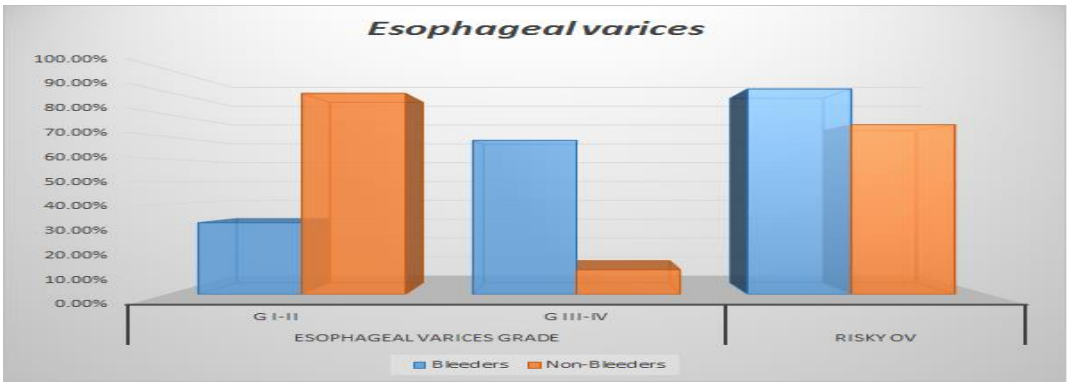

Figure (2): OV in both groups.

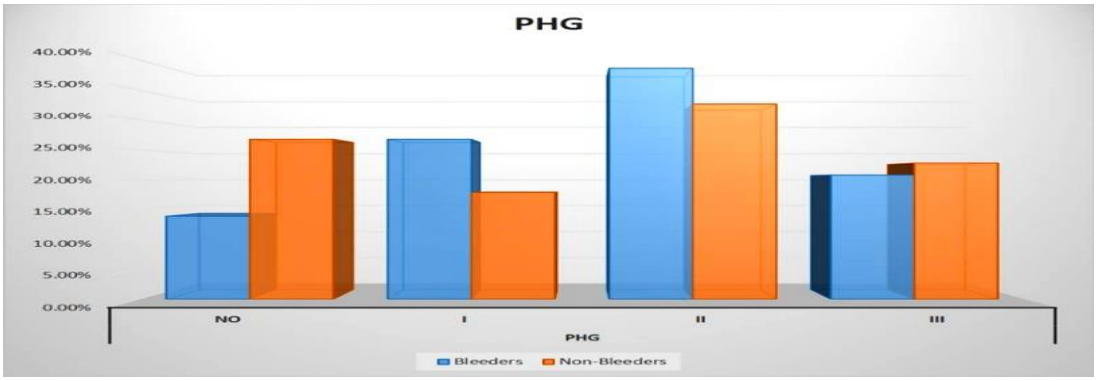

Figure (3): PHG in both groups.

Table (6): Multivariate logistic regression analysis of potential predictors of variceal hemorrhage.

Variables	β	SE	OR	95% CI	p-value	Sig.
INR	-0.77	1.14	0.5	0.0493 to 4.3803	0.503	NS
PT	0.33	0.61	1.4	0.4197 to 4.5805	0.592	NS
PVD	1.76	0.48	5.8	2.2835 to 14.7559	<0.001	HS
Child Score	-5.63	1.16	0.0	0.0004 to 0.0345	<0.001	HS
EV grades	2.13	0.23	1.4	0.6135 to 2.8735	<0.001	HS
Constant	0.059					
Null model-2 log likelihood= 270.3, overall model $\chi 2$=220, degree of freedom=7, p<0.001 (HS), Cox & snell r2=0.674, Negelkerke r2=.899, Hosmer & Lemeshow: $\chi 2$=4.8, degree of freedom=8, p=.756 (NS), Overall predicted correct percentage of the model is 94.6%						

β: regression coefficient SE: standard error OR: odds ratio; 95%
CI: 95% confidence interval P<0.001 is highly significant.
PT: Prothrombin time INR: International Normalization Ratio
PVD: Portal vein diameter EV: Esophageal varices

DISCUSSION

Esophageal varices are considered the most common cause of acute upper gastrointestinal bleeding in Egypt **[10]**. It was estimated that esophageal varices develop in about 50-63% of patients with liver cirrhosis and portal hypertension. When hepatic venous pressure gradient (HVPG) is more than 12 mmHg, acute variceal bleeding (AVB) can occur **[11,12]**.

Bleeding from esophageal varices in cirrhotic patients is considered a life threatening complication despite improvements in medical and endoscopic lines of treatment with mortality ranging from 15 to 20 % **[1]**.

INR elevation reflects the severity of protein synthetic dysfunction in acute and chronic liver disease. In liver disease, although PT is prolonged and INR is elevated, coagulation system is yet balanced. This is because of the fact that derangement of the natural coagulants is opposed by derangement of the natural anticoagulants; both of which is synthesized by the liver. So, validity of INR elevation as a marker for bleeding is questionable **[13]**.

The aim of the present study is to evaluate INR elevation as a risk factor for bleeding from esophageal varices. To achieve this goal, 202 cirrhotic patients with esophageal varices were recruited and divided into two equal groups; the first with first attack of bleeding from esophageal varices (cases) and the second without bleeding esophageal varices (controls).

Regarding age and sex, this study revealed that there is no statistically significant difference between both groups with male predominance in both groups. This result is in agreement with most of studies that compare between patients with bleeding and non-bleeding esophageal varices **[14,15,16]**. This finding can be explained by the fact of the higher prevalence of HCV infection, alcohol abuse and cigarette smoking among men.

In this study, there was no significant difference between bleeders and non-bleeders as regard non selective beta blocker (NSBB) intake. This result is in agreement with Shukla et al. **[16]** who studied cirrhotic patients on NSBB and found that 12% of them bled during 12 months of follow up and recommended continuous adjustment of the dose during primary prophylaxis and concluded that only those on higher doses of NSBB had a lower risk of variceal bleeding.

As regard sonographic data, there was a statistically highly significant difference between bleeders and non-bleeders as regard liver size, portal vein diameter, presence and degree of ascites while there was a statistically non-significant difference between both groups as regard splenic size, presence of HCC and portal vein thrombosis.

Our findings about portal vein diameter are consistent with those of Schepis et al. **[17]**, García-Tsao et al. **[2]** and Pe˜naloza-Posada et al. **[15]**. On the other hand, Ghweil et al. **[18]** reported non-significant difference between bleeders and non-bleeders as regard portal vein diameter explaining their finding by the fact that portal vein diameter might not reflect portal venous pressure.

Our findings about ascites are contradictory to those of Shukla et al. **[16]** who reported significant higher percentage of patients with ascites in bleeders than in non-bleeders, those of Nada et al. **[19]** who found that ascites is associated with presence of esophageal varices and those of Sedrak et al. **[20]** who found that ascites is associated with larg varices. Also, Limquiaco et al. **[14]** didn't report any significant difference as regard ascites between bleeders and non-bleeders. Difference in results can be attributed to the fact that most patients in our non-bleeder group were intendedly ascitic having HRS or SBP.

Our findings about HCC and portal vein thrombosis are consistent with those of Hshieh et al. **[21]** and Shukla et al. **[16]**. These findings may be attributed the facts that HCC per se has nothing to do with either development or bleeding from esophageal varices and the pressure rising effect of portal vein thrombosis may be as slow as to allow compensatory mechanisms to take place.

Our findings about splenomegaly are consistent with those of Limquiaco et al. **[14]** and Ghweil et al. **[18]**. On the other hand, splenomegaly was associated with presence of varices **[22]**, large varices **[20]** and bleeding varices **[23]**. Our findings reflect the fact that splenomegaly is not only related to portal hypertension. Hemosiderin deposition and reactive lymphocyte and endothelial cell hyperplasia are other mechanisms included in the process of splenomegaly.

As regard CBC, there was a statistically non-significant difference in platelet count between both groups. These findings are similar to those of Benedeto-Stojanov et al. **[24]** and Pe˜naloza-Posada et al. **[15]**. On the other hand, Limquiaco

et al. **[14]** and Ghweil et al. **[18]** reported a highly significant difference in presence and severity of thrombocytopenia between bleeders and non-bleeders. We attribute our findings to the fact that thrombocytopenia has nothing to do with initiation of a bleeding episode but it may have a role in defining the severity of the episode or occurrence of rebleeding.

As regard serum bilirubin and albumin, bilirubin level was significantly lower and albumin was significantly higher in bleeders than in non-bleeders. Hshieh et al. **[21]** reported similar results as regard bilirubin but reported a non-significant difference as regard albumin. Also, Limquiaco et al. **[14]** and Ghweil et al. **[18]** reported non-significant differences in serum bilirubin and albumin between bleeders and non-bleeders. We attribute our results to the fact that we selected our non-bleeder patients from a sector of patients with a greater degree of liver decompensation.

As regard INR, the median admission INR for 1.3 for bleeders and 1.9 for non-bleeders and the statistical difference was highly significant. This finding is consistent with those of Benedeto-Stojanov et al. **[24]**, Limquiaco et al. **[14]**, Hshieh et al. **[21]** and Sedrak et al. **[20]**.

This result supports the findings of previous clinical studies which concluded that INR was not valid as a measure of neither bleeding risk nor coagulopathy in cirrhotic patients **[3,4,5,21, 25,26]**. Coagulation process in liver cirrhosis is dynamic and complex as the derangement in natural coagulants is opposed by a derangement in natural anticoagulants; both of which is synthesized in the liver. INR is an accurate measure of liver synthetic function and has been well validated as a means of indicating liver decompensation and predicting mortality in cirrhotic and acute liver failure patients **[27]**.

In the present study, there was a statistically significant difference between both groups regarding grades of esophageal varices and presence of risky signs being of higher grades in bleeders. This result is in line with many researchers **[14,15,18,24,28]**. Up to our knowledge, no researcher denies the close relation between bleeding from esophageal varices and their grades and presence of risky signs.

This study does not report a significant difference between bleeders and nonbleeders as regard grades of portal hypertensive gastropathy. Mirghani and Khamees **[23]** reported presence of PHG in 32% of patients with bleeding esophageal varices and Limquiaco et al. **[14]** reported significant difference as regard presence of PHG between bleeders and non-bleeders. Difference in results can be explained by the fact that most of our non-bleeders were Child C cirrhotics where portal hypertension advances and increases the frequency of PHG.

In the present study, there was a statistically highly significant difference between bleeders and non-bleeders as regard Child score. This result is inconsistent with that of many researchers who studied the predictive factors of bleeding esophageal varices and reported non-significant difference in Child score between bleeders and non-bleeders **[14,15,24,29]**. Difference in results may be attributed to inclusion criteria adopted in our work where most of non-bleeders were admitted to hospital for management of refractory ascites and hepatic encephalopathy. As a result, non-bleeders had higher Child scores than bleeders who might have more pronounced vascular than parenchymatous decompensation.

In this study, when multivariate logistic regression analysis was done to determine the potential risk factors for bleeding esophageal varices, it revealed that elevated INR and prolonged prothrombin time were not risk factors of bleeding. This is consistent with Hshieh et al. **[21]** and Sedrak et al. **[20]**. Furthermore, in a recent prospective study, Chandail et al. **[22]** studied two groups of cirrhotic patients, with and without esophageal varices and stated that INR failed to draw association with the presence of esophageal varices. Also, Nada et al. **[19]** found that prolonged PT was not associated with neither presence of varices nor large varices.

Multivariate analysis in this study revealed that portal vein diameter was a predictor of bleeding. This result is similar to that of Pe˜naloza-Posada et al. **[15]**. Also, other researchers studied non-invasive markers for prediction of varices and found that the increase of portal vein diameter is associated with presence of varices **[22,30,31]** and with large varices **[19]**.

Also, it revealed that presence of large esophageal varices is a predictive risk factor for the occurrence of variceal bleeding and this is consistent with many researchers **[14,15,18,24, 28,32]**.

Also, it revealed that Child Pugh score was a negative predictor of bleeding esophageal varices. This is inconsistent with Sedrak et al. [**20]** and

Cherian et al. **[31]** who reported that large varices and bleeding varices were associated with higher Child scores. On the other hand, Merkel et al. **[32]**, Benedeto-Stojanov et al. **[24]**, Pe˜naloza-Posada et al. **[15]** found that hepatic dysfunction in the form of high Child classes were not related to variceal bleeding.

Difference in results can be attributed to heterogeneity of studied the patients and complexity of the confounding factors. Recruitment of homogenous groups of patients regarding age, sex, NSBB intake, liver function, kidney function, degree of portal hypertension, grade of esophageal varices and co-morbid diseases is nearly impossible in human being. In spite of these heterogeneities, the only risk factor which was confirmed as a predictor of bleeding from esophageal varices is the high grade of varices with presence of risky signs and the only factor about which studies agreed to deny its validity is the INR.

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Conflicts of interest: None.

Ethical approval: The protocol of the study was approved by the ethical committee of Faculty of Medicine, Zagazig University. Informed consents were obtained from all patients

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