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ORIGINAL ARTICLE

Role of Elevated International Normalized Ratio as a Predictor for Portal Vein Thrombosis in Cirrhotic Patients

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ABSTRACT

Background: Prothrombin time (PT) and international normalized ratio (INR) prolongation have traditionally been utilized as indications of the degree of coagulopathy in cirrhosis. Which is thought to be a hypocoagulable state. It most likely overestimates the risk of bleeding in people with liver disease. Despite the common misconception that liver cirrhosis increases the risk of bleeding, elevated INR levels may be able to predict presence of portal vein thrombosis (PVT) in cirrhotic patients, helping them to avoid the complications that come with it.. **Aim:** To assess the value of elevated INR as a predictor of occurrence of PVT in patients with cirrhosis. **Methods:** This case control study was conducted at Tropical Medicine Department, Zagazig University Hospitals. This study included one hundred thirty four (134) individuals, divided into two groups: 67 cirrhotic patients with PVT (case group) and 67 cirrhotic patients without PVT (control group). **Results:** The case group had significantly elevated INR compared to the controls. INR was a strong predictor of PVT (AUC=0.737, p<0.001), with a cut off (>1.2) showing sensitivity of 80.6%, specificity of 53.7%, PPV of 63.5%, and NPV of 73.5%. **Conclusions:** An elevated international normalized ratio may be able to predict portal vein thrombosis in cirrhotic patients. Also, INR can be used as a measure of disease severity in liver cirrhosis So, don't treat the INR, treat the patient.

Keywords: International Normalized Ratio,; Portal Vein Thrombosis; Cirrhosis

INTRODUCTION

Portal vein thrombosis (PVT) is the development of thrombus within the major portal vein (PV) or any of its branches, with or without extension into the splenic and superior mesenteric veins (SMV). About 1% of people with compensated cirrhosis, 8%–25% of people thinking about having a liver transplant, and 40% of patients with hepatocellular carcinoma (HCC), including those with tumoral PVT, have PVT. **[1, 2].**

PVT should never be ignored since it can make varices more likely to hemorrhage and make liver transplantation more challenging for people with cirrhosis. **[3].** The onset of PVT in cirrhosis patients is a significant step toward the development of severe liver disease and raises the risk of mortality. **[3].**

Changes in the portal venous system's hemodynamics are crucial to the etiology of PVT in cirrhosis. The development of fibrous tissue and the loss of hepatic sinusoids are hallmarks of cirrhosis, which increases intrahepatic resistance and reduces portal vein blood flow. A ten- to twenty-fold greater risk of PVT is linked to lowering portal vein velocity on Doppler ultrasonography to <15 cm/s, **[4].**

According to Maruyama, a flow volume >400 mL/min and a flow velocity >10 cm/s are indicative of collateral artery and PVT development in cirrhotic individuals. Non-selective beta-blockers (NSBBs) and portosystemic shunts, are two more reasons that can lower PV blood flow and perhaps result in a "steal" state. **[5].**

Patients with end-stage liver illness can develop portal vein thrombosis for a variety of reasons, but

the main ones are decreased portal blood flow and hypercoagulability. Cirrhosis has long been thought to be a hypocoagulable disorder, with the severity of coagulopathy determined by the length of prothrombin time (PT) and international normalized ratio (INR) prolongation. The INR most certainly overstated the risk of bleeding in people with liver disease, despite the fact that its primary aim was to assess hypocoagulability in patients taking vitamin K antagonists **[6].**

Because of fluctuations in the quantities of many procoagulant and anticoagulant chemicals, cirrhotic patients' coagulation systems are sensitive but rebalanced. Hemostasis in liver cirrhosis is defined by reduced levels of main coagulation factors, with the exception of factor VIII and von Willebrand factor **[7].** Additionally, there is a comparable decrease in natural anticoagulant components including protein C and S. Despite the popular idea that liver cirrhosis increases the risk of bleeding, more recent research indicates that cirrhosis actually causes a hypercoagulable condition that cannot be measured by standard coagulation tests **[2].**

METHODS

This case control study was conducted between May 2023 and October 2023 at Intensive Care Unit, Tropical Medicine Department of Zagazig University Hospitals. Every patient gave their informed permission. Approval from Zagazig University's Faculty of Medicine's ethical committee was obtained (IRB number 10458). Two groups including; 67 cirrhotic patients with PVT (case group) and 67 cirrhotic patients without PVT (control group) were created from the total of 134 patients with liver cirrhosis. Diagnosis of liver cirrhosis is according to clinical, laboratory, imaging data. Compatibility of the two groups regarding Child Pugh scores was considered between the two groups.

Inclusion Criteria in the study included patients > 18 years old with liver cirrhosis with different Child Pugh classes A&B&C either with or without portal vein thrombosis. The diagnosis of cirrhosis of the liver was made using imaging, laboratory, and clinical data. Exclusion criteria included malignant disease except HCC, current abdominal infection, usage of antiplatelet (such as aspirin, clopidogrel) and anticoagulant (such as heparin) medications, pregnancy and contraceptive pills, myeloproliferative disorders, patients with history of sclerotherapy of esophageal varices, acute and chronic pancreatitis and recent abdominal trauma in patient's history.

All participants in the study were subjected to detailed history taking with special emphasis on: age, gender, manifestations of vascular and parenchymal liver decompensation and history of drug intake (anticoagulant use), full clinical examination: General examination focusing on pulse, blood pressure, and body temperature and stigmata of chronic liver disease like palmer erythema, spider naevi, clubbing, jaundice, flapping tremors and gynecomastia, local abdominal examination searching for liver, spleen, presence of ascites and signs of portal hypertension.

The Modified Child-Pugh score for hepatic diseases was calculated **[8].** The MELD grading methodology for end-stage liver disease was utilized. The MELD score, which is a mathematical function adjusted to prioritize liver transplantation, includes bilirubin, creatinine, and the PT represented as INR. **[9].** MELD = 3.78 x [serum bilirubin (mg/dL)]. + 11.2x [INR] + 9.57x [serum creatinine (mg/dL)]. + 6.43 is the formula used to get the MELD score. If the patient has had two dialyzes in the past seven days, the serum creatinine utilization factor is 4.0. To avoid scores below zero, any value less than one is awarded a value of one (for example, if the bilirubin level is 0.8, 1.0 is utilized). This is because the natural logarithm would produce a negative result for any positive value below 1. **[10].**

Complete blood count (CBC), liver and kidney function tests, AFP, D dimer, prothrombin time, and INR were among the laboratory tests performed. Also, pelvi-abdominal ultrasonography was done by use of (Sonoscap S11) with 3.75 MHz convex probe, for evaluation of liver size, echopattern, focal lesions, portal vein diameter, patency, examination of spleen and ascites. Triphasic CT abdomen and pelvis was used to differentiate between a benign and malignant thrombus. Usually, bland thrombus is observed as a non-enhancing, low density defect in the portal veins. while neovascularization-induced intra-thrombus contrast enhancement or vessel wall distension accompanying contrast injection causes a tumor thrombus to intensify.

PVT was categorized as follows based on the thrombus's dimensions and extent: Grades 1 through 4: partial PV thrombosis, in which the thrombus covers less than 50% of the PV lumen; complete occlusion, in which the thrombus extends into the proximal and distal SMV; complete thrombosis, in which the thrombus extends to the SMV's proximal portion; and complete thrombosis, in which the thrombus covers more than 50% of the PV lumen. **[11].**

STATISTICAL ANALYSIS

Utilizing computerization and the SPSS (Statistical Package for Social Science) version 20 application, the data was statistically analyzed. The

Kolmogorov-Smirnov test was used to determine whether the data had a normal distribution. Multivariable logistic regression analysis, the U test, the Mann Whitney, Fisher exact, and Chi square test ($\chi 2$) Correlation were used.

RESULTS

Patients were divided into two groups: group 1 (case group) consisted of 67 patients with liver cirrhosis with PVT, and group 2 (control group) comprised of 67 patients with liver cirrhosis without PVT. Each group was then separated into two groups based on the child Pugh score: Group 1 (7 child class A, 27 child class B, and 33 child class C) and Group 2 (10 child class A, 32 child class B, and 25 child class C).

Group 1 had a higher MELD score and HCC than group 2, and there was a statistically significant difference in the sex distribution of the PVT patients among the examined cases. PVT patients were predominantly male. Among the groups under investigation, there was no statistically significant variation in the virological cause of liver cirrhosis (Table 1).

Platelet count and albumin levels were considerably lower in group 1 (p=0.032). Furthermore, group 1's levels of ALT, AST, INR, and total and direct bilirubin were noticeably greater than group 2's. Regarding D. Dimer levels, there was no statistically significant variation among the individuals under examination (Table 2).

Among patients with child B (p = 0.002) and C (p = 0.001), there was a statistically significant difference in INR between the analyzed groups, with group 1 having a significantly higher INR than group 2. For patients with child A score, there was no statistically significant difference in INR across the research groups. Regarding HCC among patients with child B and C, there was a statistically significant difference between the studied groups; group 1 had a significantly higher proportion of positive HCC than group 2 (p=0.028 and 0.031, respectively). For patients with a child A score, there was no statistically significant difference in HCC across the studiedl groups (Table 3).

In group 2, D-dimer showed a strong positive correlation with MELD score (r=0.694, P<0.001). However, there was no statistically significant association between D-dimer and MELD score in group 1 (Table 4).

Patients in child class A had significantly lower D-dimer levels than those in child B (p1=0.05), and both groups had significantly lower levels than patients in child C (p2<0.001, p3=0.008). The study found a strong correlation (p<0.001) between D-dimer levels and child scores in group 2. However, in group 1, there was no statistically significant difference between the child score and D-dimer. (Table 5).

The study groups had statistically significantly difference in terms of ascites; group 1 had significantly more ascites than group 2. There was a statistically significant difference (p=0.023) in the incidence of varices between the study groups; group 2 had a lower incidence of esophageal varices, whereas group 1 had a higher incidence of fundal varices. Regarding gastrointestinal bleeding and renal impairment, there was no statistically significant difference between the groups under investigation (Table 6).

The ROC curve of INR as a predictor for PVT revealed that at a cut off value of INR (>1.2) (AUC=0.737, p<0.001), sensitivity was 80.6%, specificity was 53.7%, PPV was 63.5%, and NPV was 73.5%. (Table 7; Figure 1).

Table 1: Comparison between the two studied groups according to baseline data

Demographic data	Group1 (n=67)		Group2 (n=67)		Test of sig.	P
	No.	%	No.	%		
Sex						
Male	52	77.6	38	56.7	χ^2= 6.632	0.010*
Female	15	22.4	29	43.3		
Age (years)						
Range (Min. –Max.)	39.0 – 82.0		42.0 – 90.0		T= 0.751	0.454
Mean ± SD.	62.52 ± 8.34		63.70 ± 9.77			
Virology						
Negative	13	19.4	14	20.9	2.123	0.517
HCV	54	80.6	51	76.1		
HBV	0	0	2	3		
MELD score Range (Min. – Max.)	7.0 – 34.0		6.0 – 29.0		1592.500*	0.004*
Median (IQR)	18.0 (12.0 –25.0)		15.0 (9.0 – 20.0)			
HCC Negative	27	40.3	45	67.2	9.726*	0.002*
Positive	40	59.7	22	32.8		

SD: **Standard deviation**, χ^2: **Chi square test, t: Student t-test, MC: Monte Carlo**
P: p value for comparing between **the two studied groups**
*: Statistically significant at $p \leq 0.05$.

Table 2: Comparison between the two studied groups according to laboratory investigations.

	Group 1 (n=67)	**Group 2 (n=67)**	**U**	**P**
Hemoglobin (g/dl)				
Range (Min. – Max.)	4.3 – 15.2	5.7 – 13.8	2237	0.973
Median (IQR)	9.3 (8.1 - 11.1)	9.4 (8.2 - 11)		
WBCs (x10^{3}cells/µl)				
Range (Min. – Max.)	1.6 – 21	2.4 – 19	2170.5	0.742
Median (IQR)	6.7 (4.6 - 8.9)	6.2 (4.4 - 9)		
Platelets (x10^{3}cells/µl)				
Range (Min. – Max.)	25 – 410	27 – 335	1763*	0.032*
Median (IQR)	102 (60 - 150)	140 (81 - 182)		
Creatinine	**(n=67)**	**(n=67)**		
Range (Min. – Max.)	0.37 – 3.50	0.21 – 5.90	U= 2218.500	0.908
Median (IQR)	1.0 (0.73 – 1.50)	1.0 (0.75 – 1.41)		
BUN Range (Min. – Max.) Median (IQR)	**(n=67)** 7.5 - 95 24.9 (16.8 - 46.8)	**(n=67)** 7.7 - 95 23.9 (15.7 - 42.2)	U= 2093.5	0.502
Total Bilirubin	**(n=64)**	**(n=67)**		
Range (Min. – Max.)	0.34 – 27.0	0.12 – 19.0	U= 1441.500*	0.001*
Median (IQR)	2.0 (1.27–6.11)	1.38 (0.83–2.14)		
Direct bilirubin	**(n=63)**	**(n=67)**		
Range (Min. – Max.)	0.10 – 25.0	0.09 – 79.0	U= 1465.500*	0.003*
Median (IQR)	1.30 (0.61–4.76)	0.60 (0.33–1.55)		
Albumin	**(n=67)**	**(n=67)**		
Range (Min. – Max.)	1.50 – 4.60	1.79 – 4.90	U= 2.655*	0.009*
Mean ± SD.	2.69 ± 0.62	2.98 ± 0.63		
ALT Range (Min. – Max.) Median (IQR)	**(n=67)** 10 - 1558 30 (19 - 50)	**(n=67)** 8 - 228 23 (15 - 39)	U= 1704.5*	0.016*
AST Range (Min. – Max.) Median (IQR)	**(n=67)** 1.3 – 1208 62 (34 - 117)	**(n=67)** 1.3 - 270 41.4 (26 - 62)	U= 1589.5*	0.004*
Na	**(n=67)**	**(n=67)**		
Range (Min. – Max.)	116.0 – 142.0	120.0 – 144.0	T= 1.223	0.223
Mean ± SD.	133.19 ± 5.77	134.37 ± 5.38		
INR Range (Min. – Max.)	1.05 – 2.33	0.96 – 1.80	5.384*	<0.001*
Mean ± SD.	1.44 ± 0.27	1.23 ± 0.18		
D. Dimer Range (Min. – Max.)	0.40 – 30.0	0.40 – 22.70	1910.0	0.136
Median (IQR)	5.0 (3.0 – 10.0)	4.50 (2.30–7.0)		

IQR: **Inter quartile range** **U: Mann Whitney test, t: Student t-test**
P: p value for comparing between **the two studied groups**
*: Statistically significant at $p \leq 0.05$

Table 3: Comparison between the two studied groups according to INR and HCC in in different classes of child Pugh score

	Group 1		Group 2		T	P
INR						
Child A	**(n=7)**		**(n=10)**			
Range (Min. – Max.)	1.1 - 1.45		0.96 - 1.33		2.068	0.056
Mean ± SD.	1.26 ± 0.14		1.11 ± 0.14			
Child B	**(n=27)**		**(n=32)**			
Range (Min. – Max.)	1.05 – 1.98		0.98 - 1.8		3.225*	0.002*
Mean ± SD.	1.37 ± 0.25		1.19 ± 0.16			
Child C	**(n=33)**		**(n=25)**			
Range (Min. – Max.)	1.22 - 2.33		1.01 - 1.7		3.695*	0.001*
Mean ± SD.	1.54 ± 0.28		1.32 ± 0.16			
HCC						
Child A	**(n=7)**		**(n=10)**			
Negative	4	57.1	7	70.0	0.298	^{Fe}p= 0.644
Positive	3	42.9	3	30.0		
Child B	**(n=2٧)**		**(n=٣٢)**			
Negative	10	37.0	21	65.6	4.8*	0.028*
Positive	17	63.0	11	34.4		
Child C	**(n=٣٣)**		**(n=٢٥)**			
Negative	13	39.4	17	68.0	4.661*	0.031*
Positive	20	60.6	8	32.0		

SD: **Standard deviation** **t: Student t-test**
P: p value for comparing between **the two studied groups**
*: Statistically significant at $p \leq 0.05$

Table 4: Correlation between D. Dimer and MELD score in each group.

MELD score	D. Dimer	
	R_s	P
Group 1 (n=67)	0.227	0.064
Group 2 (n=67)	0.694*	<0.001*

R_s: Spearman coefficient
*: Statistically significant at $p \leq 0.05$

Table 5: Relation between D. Dimer and Child score among both groups.

Child score	N	D. Dimer		H	P
		Range (Min. – Max.)	Median (IQR)		
Group 1 (n=67)					
Child A	**7**	2 – 8	3.4 (2.5 - 4)	4.480	0.106
Child B	**27**	0.4 – 30	4 (2.5 - 11)		
Child C	**33**	0.5 - 30	6.5 (3.65 - 10.5)		
Group 2 (n=67)					
Child A	**10**	0.4 – 5	2.3 (0.88 - 3.38)	15.913*	<0.001*
Child B	**32**	0.7 – 22.7	3.5 (1.8 – 5.95)		
Child C	**25**	1.8 - 22	5.5 (4.3 – 12.75)		
		P1=0.05*, P2<0.001*, P3=0.008*			

IQR: **Inter quartile range** H: H for **Kruskal Wallis test**
P: p value for comparing between **the studied categories**
*: Statistically significant at $p \leq 0.05$
P1: Comparison between child A&B groups
P2: Comparison between child A&C groups
P3: Comparison between child B&C groups

Table 6: Comparison between the two studied groups according to ascites, hepatic encephalopathy (HE), varices, GIT bleeding and renal impairment.

	Group1 (n=67)		Group2 (n=67)		X^2	P
	No.	%	No.	%		
Ascites						
No ascites	13	19.4	22	32.8	10.657*	0.014*
Mild	10	14.9	14	20.9		
Moderate	33	49.3	15	22.4		
Severe	11	16.4	16	23.9		
HE						
No HE	33	49.3	36	53.7	1.055	0.590
Once HE	18	26.9	13	19.4		
Recurrent HE	16	23.9	18	26.9		
Varices						
No varices	28	41.8	24	35.8	9.503*	0.023*
Esophageal varices	22	32.8	35	52.2		
PHG	6	9.0	6	9.0		
Fundal varices	11	16.4	2	3.0		
GIT bleeding						
NO	17	25.37%	22	32.8%	1.596	>0.10
Once	23	34.3%	20	29.9%		
Recurrent	27	40.3%	25	37.3%		
Renal impairment						
<1.5	49	73.13 %	52	77.6 %	0.773	>0.25
=>1.5	18	26.8 %	15	22.3 %		

P: p value for comparing between **the two studied groups**
*: Statistically significant at $p \leq 0.05$

Table 7: Diagnostic performance of INR for the prediction of PVT

	Cut-off	Sensitivity	Specificity	PPV	NPV	AUC	p value
INR	>1.2	80.6	53.7	63.5	73.5	0.737	<0.001*

PPV: Positive predictive value, NPV: Negative predictive value, AUC: Area under the ROC curve
*: Statistically significant at $p \leq 0.05$

DISCUSSION

In the present study, there was no statistically significant variation in age (Mean age 62.52±8.34 in patients with PVT and 63.70 ± 9.77 in patients without PVT) and a statistically significant difference in terms of sex, with a male predominance in both groups. **Then et al. found that [12]** There was no statistically significant difference between the two groups based on age or gender. in his study on PVT in liver cirrhosis.

The two groups' virological etiologies of cirrhosis showed no statistically signinficant difference, with a prevalence of the hepatitis C virus in each. In our study, the hepatitis C virus was present in 76.1% of patients without PVT and 80.6% of patients with PVT. Also, **Then et al. [12] recorded** in his research that, the majority of patients 49% in the control group and 50% in the research group in both groups had cirrhosis as a result of hepatitis C. This did not align with **Cagin et al. [13]**, where, the majority of patients in his study (45.9%) had cirrhosis associated with the hepatitis B virus (HBV), and the distribution of etiologies was similar throughout the groups.

Regarding MELD score, there was a statistically significant difference between the examined instances (median 18 in individuals with PVT versus 15 in those without PVT) as MELD score is a result of multiplying INR by serum creatinine by serum bilirubin and most of patients in our study has high INR. This result is consistent with **Berry et al. [14]** but not consistent with **Then et al. [12],** found that although patients with PVT had a mean MELD score that was greater among pvt patients than that of patients without portal thrombosis, these differences were not statistically significant.

Regarding CBC, there was no statistically significant difference between both groups regarding Hemoglobin but Platelet count was

significantly decreased in group 1 than group 2 (p=0.032). This is not consistent with **Then et al. [12]** study that showed Patients with PVT show a statistically significant rise in platelet count (P value = 0.0001) unlike **Chen et al. [15], t**hey found that blood platelet counts and Hemoglobin levels in PVT patients were significantly lower than in non-PVT people (P<0.01).

Our study showed that group 1 had significantly increased total and direct bilirubin (p=0.001, 0.003) which was consistent with **Then et al. [12].** On the other hand, albumin level was significantly decreased in group 1 than group 2 (p=0.009) which was not consistent with **Then et al. [12]** but is consistent with **Huang et al. [16]** and **Basili et al. [17]** They found that PVT is linked to low serum albumin in liver cirrhosis, implying that albumin may modulate the hemostatic system by interfering with processes controlling platelet activation.

Moreover in our study, regarding serum Na levels, There was no significant difference between the two groups (p = 0.908). This conclusion was consistent with **Berry et al. [14]** study, which found that patients with PVT were similar to those without PVT, but not with **Then et al. [12]** who,found that sodium was much lower in PVT patients than in non-PVT patients, suggesting that hyponatremia is a measure of cirrhosis severity.

A statistically significant difference (59.7% in patients with PVT and 32.8% in patients without PVT) was seen in the HCC cases in both groups. This was consistent with **Cagin et al. [13]** in a study that demonstrated a strong positive connection (P<0.01) between PVT and hepatocellular carcinoma (HCC).

Group 1 had a considerably larger proportion of patients with positive HCC than group 2, demonstrating a statistically significant difference in HCC and child Pugh score between the examined groups among patients with child B and C (p=0.028, 0.031, respectively), indicating that PVT and HCC are strongly related to the severity of liver dysfunction. For patients with a child A score, there was no statistically significant difference in HCC between study groups.

The degree of ascites varied statistically significantly between the groups under study; group 1 had considerably more ascites than group 2 (p=0.014). This is in agreement with **Berry et al. [14]** and **Stine et al. [18]** in his meta-analysis study that showed that PVT was associated with an increased risk of ascites. This result of the current study confirmed that PVT is a biovatal factor for localizing of ascites. This was not consistent with **Cagin et al. [13]** according to a research that found no statistically significant variation in ascites between the groups.

Because hepatic encephalopathy is associated with liver dysfunction, the incidence of the disease did not differ statistically significantly among the groups under investigation. Given that HE is associated with liver disease severity. The results of **Cagin et al. [13]** showed no statistically significant differences in the groups regarding hepatic encephalopathy.

Group 1 had a larger incidence of fundal varices than Group 2, with 16.4% versus 3%, and there was a statistically significant difference (p=0.023) between the two groups. A study that showed no statistically significant changes in the groups' disorderds, including esophageal varices, this was contradictory with **Cagin et al. [13].** Despite the fact that PVT patients experienced gastrointestinal bleeding more frequently, there was no statistically significant variation in the frequency of GIT hemorrhage among the study groups.

There was no statistically significant difference in renal impairment across the groups under investigation despite the fact that patients with PVT had higher degrees of renal impairment (18 versus 15 had serum Creatinine > 1.5).

After clot degeneration, D-dimer, a fibrin degradation product, is detected in the bloodstream. D-dimer readings are used to estimate the length of patients' anticoagulant therapy as well as the chance of recurrent venous thromboembolism **[19].** In terms of D.dimer, there was no statistically significant difference between the cases studied, despite that patients with PVT had a higher level of D.dimer (median 5) than those without PVT (median 4). These findings do not agree with **Dai et al. [20**] they discovered that D-dimer levels can be utilized to predict the incidence of portal vein thrombosis in liver cirrhosis and are strongly associated with the development of portal vein thrombosis after splenectomy.

Group 2 showed a substantial positive correlation (r=0.694, P<0.001) between MELD score and D.dimer. The MELD score and D-dimer did not, however, show a statistically significant correlation in group 1. D-dimer levels were also examined by **El-Sayed et al. [21]** in 67 patients with chronic liver disorders and 30 healthy controls. In individuals with liver cirrhosis, they found a strong correlation between D-dimer levels and MELD and Child-Pugh scores. His results showed that D-dimer levels were considerably greater in cirrhotic patients with Child-Pugh categories A and B than in non-cirrhotic patients and healthy controls.

In comparison to patients without PVT (median Child class A 2.3, Child class B 3.5, and Child class

C 5.5), patients with PVT exhibited greater degrees of D.dimer (median Child class A 3.4, Child class B 4, and Child class C 6.5). In group 2, there was a statistically significant relation between D-dimer and child score ($p<0.001$), with patients with child A class being have significantly lower D-dimer levels than those with child B ($p1=0.049$).

When comparing INR, between the patient groups in the study groups and the Child Pugh score, there was a statistically significant difference with child class B ($p=0.002$) and child class C ($p=0.001$), with group 1 having a substantially higher INR than group 2. There was also a statistically significant difference in INR between the examined cases (median 1.44 in patients with PVT vs 1.23 in individuals without). The study discovered no statistically significant variation in INR between groups of individuals with child class A. These findings are consistent with **Then et al. [12],** who discovered that PVT was associated with higher INR values in cirrhotic individuals, **Cagin et al. [22**], who stated that PVT is most likely the cause of rising INR levels, and **Dabbagh et al. [23],** who demonstrated that individuals with cirrhosis did not have a lower risk of thrombosis when their INR level was higher. These findings suggest that INR can be utilized as a prognostic indicator rather than a marker of bleeding risk in cirrhotic patients.

The ROC curve study revealed that INR as a predictor of PVT (AUC=0.737, $p<0.001$), at a cut off (>1.2) had a sensitivity of 80.6%, specificity of 53.7%, PPV of 63.5%, and NPV of 73.5%.

CONCLUSIONS

An elevated international normalized ratio may be able to predict portal vein thrombosis in cirrhotic patients. In addition, INR can be used as a measure of disease severity in liver cirrhosis. So, do not treat the INR, treat the patient.

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REFERENCES

1. Sarin SK, Philips CA, Kamath PS, Choudhury A, Maruyama H, Nery FG, & Valla DC. Toward a comprehensive new classification of portal vein thrombosis in patients with cirrhosis. Gastroenterol 2016; 151(4), 574-77.
2. Intagliata NM, Argo CK, Stine JG, Lisman T, Caldwell SH, Violi F. Concepts and controversies in haemostasis and thrombosis associated with liver disease: proceedings of the 7th International Coagulation in Liver Disease Conference. Thromb Haemost, 2018; 118(8):1491-1506.
3. Stine JG, Shah NL, Argo CK, Pelletier SJ, Caldwell SH, Northup PG. Increased risk of portal vein thrombosis in patients with cirrhosis due to nonalcoholic steatohepatitis. Liver Transpl 2015; 21:1016–21.
4. Stine JG, Wang J, Shah PM, Argo CK, Intagliata N, Uflacker A, et al. Decreased portal vein velocity is predictive of the development of portal vein thrombosis: a matched case-control study. Liver Int. 2018; 38(1):94-101.
5. Maruyama H, Okugawa H, Takahashi M, Yokosuka O. De novoportal vein thrombosis in virus-related cirrhosis: predictive factors and long-term outcomes. Am J Gastroenterol 2013; 108(4), 568-74.
6. Arjal R, Trotter JF. International normalized ratio of prothrombin time in the model for end-stage liver disease score: an unreliable measure. Clin Liver Dis Journal 2009; 13(1), 67-71.
7. Tripodi A, Primignani M, Lemma L, Chantarangkul V, Dell'Era A, Iannuzzi F, et al. Detection of the imbalance of procoagulant versus anticoagulant factors in cirrhosis by a simple laboratory method. Hepatol 2010; 52(1), 249-55.
8. Pugh RNH, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973; 60(8): 646-49.
9. Tripodi A, Caldwell SH, Hoffman M, Trotter JF, Sanyal AJ. The prothrombin time test as a measure of bleeding risk and prognosis in liver disease. Aliment. Pharmacol. Ther 2007; 26(2): 141-48.
10. Kamath PS, Kim RW. The model for end-stage liver disease (MELD). Hepatol 2007; 45(3): 797-805.
11. Yerdel MA, Gunson B, Mirza D, Karayalçin K, Olliff S, Buckels J, et al. PORTAL VEIN THROMBOSIS IN ADULTS UNDERGOING LIVER TRANSPLANTATION: Risk Factors, Screening, Management, and Outcome: 1. Transplant 2000; 69(9):1873-81.
12. Then EO, Are VS, Lopez-Luciano M, Bijjam R, Ofosu A, Culliford A, et al. Elevated international normalized ratio: a risk factor for portal vein thrombosis in cirrhotic patients. J. Gastroenterol 2019; 12(3): 135.
13. Cagin YF, Atayan Y, Erdogan MA, Dagtekin F, Colak C. Incidence and clinical presentation of portal vein thrombosis in cirrhotic patients. HBPD INT 2016; 15(5): 499-503.
14. Berry K, Taylor J, Liou IW, Ioannou GN. Portal vein thrombosis is not associated with increased mortality among patients with cirrhosis. J Gastroenterol Hepatol 2015; 13(3): 585-93.
15. Chen H, Trilok G, Wang F, Qi X, Xiao J, Yang C. A single hospital study on portal vein thrombosis in cirrhotic patients-clinical

characteristics & risk factors. Indian J. Med. Res 2014; 139(2): 260-66.
16. Huang X, Fan X, Zhang R, Jiang S. Yang K, Chen S. Systemic inflammation and portal vein thrombosis in cirrhotic patients with gastroesophageal varices. Eur J Gastroenterol Hepatol 2020; 32(3): 401-5.
17. Basili S, Carnevale R, Nocella C, Bartimoccia S, Raparelli V, Talerico G, et al. Serum albumin is inversely associated with portal vein thrombosis in cirrhosis. Hepatol. Commun 2019; 3(4): 504-12.
18. Stine JG, Shah PM, Cornella SL, Rudnick SR, Ghabril MS, Stukenborg GJ, et al. Portal vein thrombosis, mortality and hepatic decompensation in patients with cirrhosis: A meta-analysis. World J. Hepatol 2015; 7(27): 2774.
19. Palareti G, Cosmi B, Legnani C, Antonucci E, De Micheli V, Ghirarduzzi A, et al. D-dimer to guide the duration of anticoagulation in patients with venous thromboembolism: A management study. Blood 2014; 124:196–203.
20. Dai J, Qi X, Li H, Guo X. Role of D-dimer in the Development of Portal Vein Thrombosis in Liver Cirrhosis: A Meta-analysis. Saudi J Gastroenterol. 2015; 21:165–74.
21. El-Sayed R, El-Karaksy H, El-Raziky M, El-Hawary M, El Koofy N, Helmy H, et al. Assessment of coagulation and fibrinolysis in children with chronic liver disease. Blood Coagul Fibrinolysis 2013; 24(2): 113-17.
22. Cagin YF, Bilgic Y, Berber İ, Yildirim O, Erdogan MA, Firat F, et al. The risk factors of portal vein thrombosis in patients with liver cirrhosis. Exp Ther Med 2019; 17(4): 3189-94.
23. Dabbagh O, Oza A, Prakash S, Sunna R, Saettele TM. Coagulopathy does not protect against venous thromboembolism in hospitalized patients with chronic liver disease. Chest 2010; 137:1145–49.

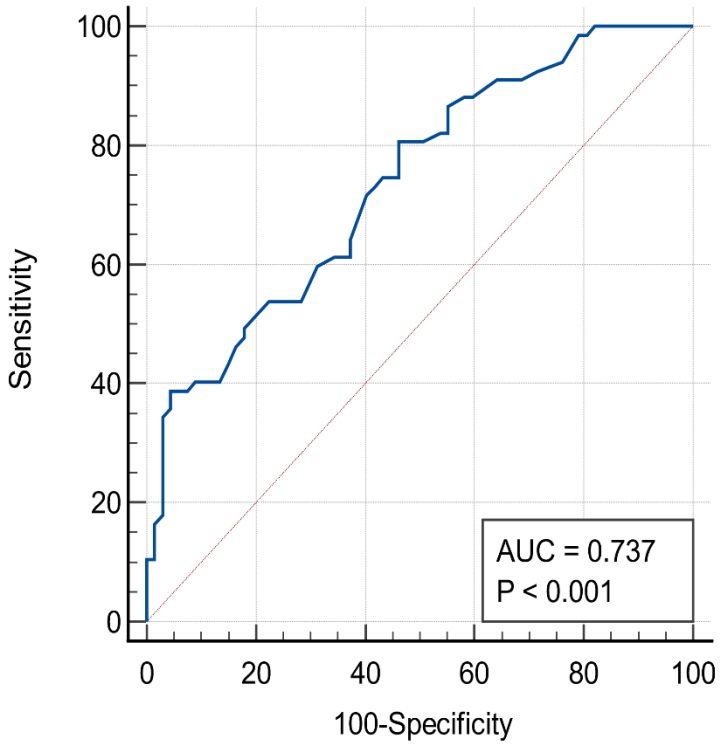

Figure 1S: ROC curve of INR for the prediction of PVT

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