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Immature Platelet Fraction as a Non-Invasive Marker for Esophageal Varices

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: All cirrhotic patients should be screened for oesophageal varices (OV) at the time of diagnosis. The development of a non-invasive method for the detection of OV is a vital issue in subjects with cirrhosis to decrease the need for invasive endoscopic procedures that can be costly. This work aimed to evaluate immature platelet fraction (IPF) as a non-invasive marker and predictor of OV.
Methods: This cross-sectional study was carried out on 80 cirrhotic patients with esophageal varices diagnosed by upper endoscopy. They were divided into Group (1): 40 patients with cirrhosis with esophageal varices and Group (2): 40 patients with cirrhosis and without esophageal varices. All patients were subjected to the complete history taking, physical examination, routine laboratory investigations (Complete blood count, IPF, C-reactive protein, Liver and kidney function tests, Bone marrow aspiration for some cases, Ascetic sample analysis when applicable), Pelvic-Abdominal ultrasonography, Child Pugh score assessment, Upper GIT endoscopy.
Results: There was a significant difference between the studied groups regarding IPF ($p<0.001$). At cutoff >12 IPF had (AUC= 0.993) with sensitivity of 97.5% and specificity of 97.5% for detection of esophageal varices. There was a significant negative correlation between IPF and platelets count (p- value < 0.001). There was a significant positive correlation between IPF and Child Pugh

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score (p- value <0.001). There was a highly significant positive correlation between IPF and CRP (p value <0.001). There was significant difference between the two groups as regards splenic longitudinal diameter (p<0.001). As regards platelet count, there was a significant difference between the two groups (p<0.001). It was significantly lower in Group 1.
Conclusions: IPF is elevated in cirrhotic patients with naive esophageal varices than in cirrhotic patients without varices. IPF could be used as a noninvasive, easy to measure method for detection of the presence of esophageal varices at a cutoff level of >12.

Keywords: Cirrhosis; immature platelet fraction; non-invasive assessment; esophageal varices.

1. INTRODUCTION

Cirrhosis is defined as the histological development of regenerative nodules surrounded by fibrous bands in response to chronic liver injury which leads to portal hypertension and other complications such as esophageal varices (OV), ascites, spontaneous bacterial peritonitis or hepatorenal syndrome [1].

OV are extremely dilated sub-mucosal veins in the lower third of the esophagus. They are most often a consequence of portal hypertension, commonly due to cirrhosis. OV are typically diagnosed through an esophagogastroduodenoscopy [2].

The term reticulated platelets describes immature platelets that contain remnants of RNA which are measured as immature platelet fraction (IPF) using automated blood cell analyzer [3].

IPF is a cheap test and related to the existence of esophageal varices as a complication from portal hypertension. Due to the invasive nature of upper endoscopy many studies search for non-invasive markers of OV, the IPF was found to be significantly useful in chronic liver disease and its complications especially OV [4].

There are however no studies investigating the role of the IPF in detecting complications of cirrhosis. Therefore, we aimed to study the IPF as a non-invasive marker for detecting OV.

The aim of this work was to assess the value of IPF as a non-invasive marker for the presence of OV.

2. PATIENTS AND METHODS

This cross sectional study was conducted on 80 cirrhotic patients diagnosed by ultrasound presenting to department of Tropical Medicine and Infectious diseases Tanta University Hospital. Patients were divided into the two groups: Group (1): 40 patients with cirrhosis and with OV. Group (2): 40 patients with cirrhosis and without OV.

2.1 Inclusion Criteria

- Cirrhotic patients whatever the etiology.
- Patients with or without OV diagnosed by upper endoscopy.
- patients with upper gastrointestinal endoscopy performed within 2 days of the IPF determination

2.2 Exclusion Criteria

- Acute bleeding.
- Bone marrow disease.
- Malignant disease including HCC.

All patients were subjected to the following:

a) Full history taking and examination: A detailed history was taken and full clinical examination was done
b) Laboratory investigations:

- Complete blood count (CBC): CBC analyses were performed with the use of Erma PCE-210 hematology analyzer to show the following indices: Hemoglobin, Platelet count and WBCs: total and differential
- Liver function profile [Serum bilirubin (direct and indirect), Alanine transaminase (ALT), Aspartate transaminase (AST), Serum albumin (By Conelab prime 60 I automated chemistry analyzer), prothrombin time and concentration and International normalized ratio (INR) (by Systemex)
- Renal function tests: Blood urea and serum creatinine (by Conelab prime 60 I automated chemistry analyzer)
- Serum C - reactive protein (CRP) by latex agglutination method.
- IPF by Sysmex XE-5000 hematology analyzer.

- Bone marrow aspiration for some cases.
- Ascitic sample analysis when applicable.

c) Radiological investigations:

Pelvic-Abdominal ultrasonography:

Real time abdominal ultrasonography was done using Hitachi EUB 515 or Toshiba SSA-340A machine with a 3.5 MHZ convex linear transducer.

Conventional ultrasonographic evaluation included:

1) The appearance of the liver as regards size (average, enlarged or shrunken), echopattern (normal, bright, coarse, established cirrhosis and heterogonous).
2) Evaluation of hepatic focal lesions (number, size, location, echogenicity, capsulation, contact with the hepatic capsule or major hepatic vessels).
3) The portal vein diameter and patency.
4) Scanning of the spleen as regards size (whether average or enlarged), textural changes and the presence of focal lesion were studied.
5) Examination of ascites (amount, whether clear or not, presence of adhesions).
6) CBD (common bile duct) dilatation and IHBRD (intrahepatic biliary radical dilatation).
7) Enlarged abdominal lymph nodes.

d) Upper GIT endoscopy: using modified Paquet classification for grading of OV.
e) Child Pugh score assessment.

2.3 Statistical Analysis

Statistical analysis was done by SPSS v25 (IBM Inc., Chicago, IL, USA). Normality of data was checked with Shapiro-Wilks test and histograms. Numerical variables were presented as mean and standard deviation (SD) and compared between the two groups utilizing Student's t- test. Categorical variables were presented as frequency and percentage (%) and were analysed utilizing the Chi-square test or Fisher's exact test when appropriate. Pearson's correlation coefficient was used to test association between OV, IPF and other studied variables. The overall diagnostic performance of each test was assessed by Receiver Operating Characteristic (ROC) curve analysis The level of significance was adopted at $P < 0.05$.

3. RESULTS

As regarding the age and sex distribution there was no significant difference between the patients of studied groups.

There were statistically significant differences in regards to clinical data between two studied groups. The predominant clinical features within cirrhotic patients with OV group were Ascites, which was reported in 30 patients (75%), lower limb edema, which was reported in 30 patients (75%), Jaundice, which was reported in 17 patients (42%) and hepatic encephalopathy was reported in 14 patients (35%). Within cirrhotic patients without OV group Ascites, lower limb edema, Jaundice which were reported in 2 patients (5%), 6 patients (15%), 2 patients (5%) respectively (Fig. 1).

There was a significant difference between studied groups as regards Child pugh score, Child A reported in 8 patients (20%), Child B reported in 15 patients (37.5%), Child C reported in 17 patients (42.5%), where in cirrhosis without varices group, Child A reported in 34 patients (85%), Child B reported in 6 patients (15%) (P-value=<0.001).

There was a significant difference between studied groups as regards grading of ascites by ultra sound.

Table 1. Age and sex of the studied groups

	Group 1 (n = 40)			Group 2 (n = 40)			t	P-value
Age (years)								
Range	40	-	76	28	-	72	1.669	0.099
Mean ±SD	55.925	±	8.786	52.275	±	10.687		
Sex								
Male	26 (65%)			20 (50%)			1.841	0.175
Female	14 (35%)			20 (50%)				

T: Student T test, X^2: Chi square test

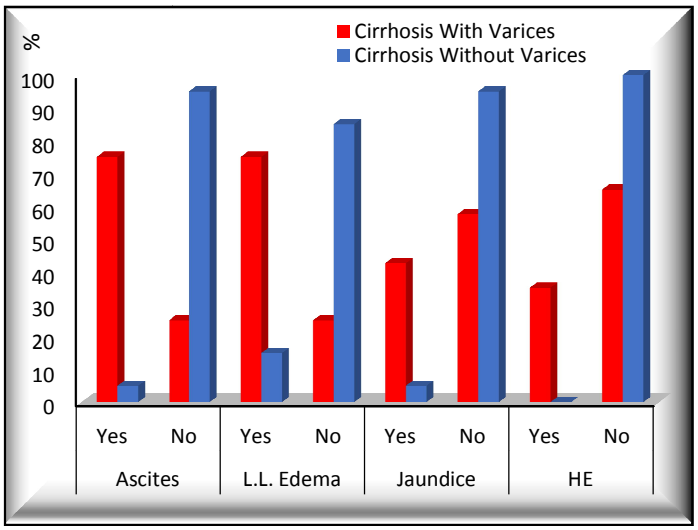

Fig. 1. Comparison between the two groups regarding clinical data

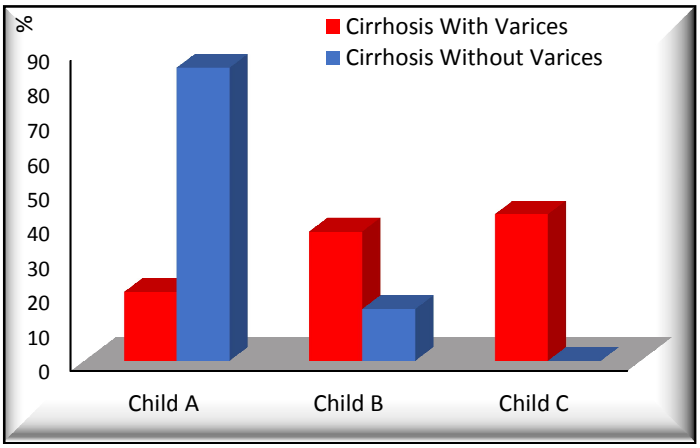

Fig. 2. Child score distribution among patient groups

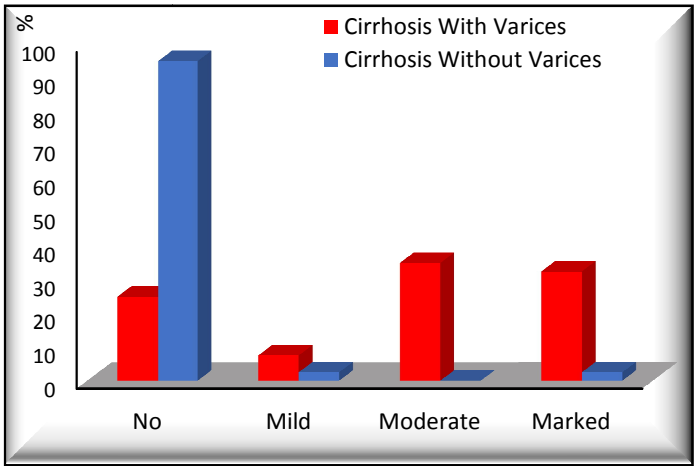

Fig. 3. Comparison between the two groups regarding grading of ascites by ultra sound

There was no significant difference between the studied groups as regards Hb and WBCs (p-value > 0.05). As regards platelet count, there was a highly significant difference between the two groups (p<0.001). It was significantly lower in Group 1.

There was no significant difference between the two groups as regards ALT and AST levels (p-value > 0.05). There was a highly significant difference between the two groups as regards Serum albumin, Total and direct bilirubin and INR (p<0.001). Serum albumin was significantly lower in Group1 while total bilirubin; direct bilirubin and INR were significantly higher in Group1. There was no significant difference between the two groups as regards creatinine, urea level (p-value > 0.05).

There was a highly significant difference between the two groups as regards CRP (p<0.001). There was a highly significant difference between the two groups as regards IPF (p<0.001). There was a highly significant difference between the two groups as regards splenic longitudinal diameter (p<0.001).

There was a highly significant correlation between IPF, Platelets count and Child pugh score. There was a highly significant negative correlation between IPF and platelets count (p-value < 0.001). There was a highly significant positive correlation between IPF and Child pugh score (p- value < 0.001). There were no correlations between IPF and markers of synthetic functions of liver such as albumin and prothrombin time.

Table 2. Comparison between the two groups concerning complete blood count

		Groups						T-Test	
		G1			G2			t	P-value
Hb (12-16g/dl)	Range	7	-	13.3	6.3	-	14.1	-1.620	0.109
	Mean ±SD	9.790	±	1.445	10.523	±	2.468		
Platelets (150-450 × 103µl)	Range	23	-	182	18.8	-	298	-7.189	<0.001*
	Mean ±SD	92.325	±	33.138	164.920	±	54.597		
TLC (4-11 × 103/mm3)	Range	1.8	-	9.8	1.9	-	10.5	-1.516	0.134
	Mean ±SD	4.893	±	2.342	5.670	±	2.245		

*t- Student t test or Man Whitney was used according to data distribution *: Statistically significant at p ≤ 0.05*

Table 3. Liver and kidney function tests and coagulation profile among the studied groups

		Group 1 (n = 40)			Group 2 (n = 40)			t	P-value
AST (up to 37 u/l)	Range	8	-	93	6.5	-	95	-0.059	0.953
	Mean ±SD	47.100	±	20.642	47.388	±	22.895		
ALT (up to 37 u/l)	Range	17	-	70	18	-	80	-1.566	0.121
	Mean ±SD	33.300	±	14.631	38.750	±	16.438		
S. Albumin (3.5-5.5 gm/dl)	Range	1.7	-	3.8	2.5	-	4.7	-9.943	<0.001*
	Mean ±SD	2.623	±	0.512	3.748	±	0.500		
T. Bilirubin (0.2-1.2 mg/dl)	Range	0.4	-	3.9	0.3	-	1.2	7.849	<0.001*
	Mean ±SD	1.615	±	0.725	0.673	±	0.226		
D. Bilirubin (up to 0.3mg/dl)	Range	0.2	-	2.3	0.1	-	0.7	7.592	<0.001*
	Mean ±SD	0.865	±	0.412	0.335	±	0.159		
INR (1-1.3)	Range	1	-	3	1	-	1.9	6.012	<0.001*
	Mean ±SD	1.592	±	0.399	1.158	±	0.222		
Serum creatinine (0.2- 1.2 mg/dl)	Range	0.5	-	2.6	0.4	-	2.4	1.529	0.130
	Mean ±SD	1.195	±	0.493	1.027	±	0.491		
Blood urea (15-50 mg/dl)	Range	28	-	100	27	-	95	1.928	0.058
	Mean ±SD	57.075	±	26.552	46.550	±	22.078		

*t- Student t test or Man Whitney was used according to data distribution *: Statistically significant at p ≤ 0.05*

Table 4. Comparison between the two groups regarding CRP, Immature platelet fraction and Splenic longitudinal diameter

		Group 1 (n = 40)	Group 2 (n = 40)	t	P-value
CRP (<6 mg/l)	Range Mean ±SD	12 - 36 23.925 ± 9.501	12 - 24 12.680 ± 2.678	7.204	<0.001*
Immature platelet fraction (1.1-6.1%)	Range Mean ±SD	10 - 35 23.69 ± 6.489	5- 16 7.783 ± 2.018	14.806	<0.001*
Splenic longitudinal diameter(cm)	Range Mean ±SD	13.5 - 24 17.25 ± 2.455	11 - 19.5 13.538 ± 1.596	8.019	<0.001*

*t- Student t test *: Statistically significant at p ≤ 0.05. CRP: C-reactive protein*

Table 5. Correlations between immature platelet fraction, platelets count and child pugh score

	Immature platelet fraction			
	Group 1(n = 40)		Group 2 (n = 40)	
	r	P-value	r	P-value
Platelets count	-0.590	<0.001*	-0.392	0.012*
Child Pugh score	0.505	0.001*	0.632	<0.001*
CRP	0.733	<0.001*	0.230	0.154

**: Statistically significant at p ≤ 0.05*

There was a highly significant positive correlation between IPF and CRP (p- value < 0.001).

When using the Receiver Operator Characterizing (ROC) curve, at cutoff >12 IPF had sensitivity of 97.5%, specificity of 97.5%, PPV of 97.5%, NPV of 97.5% and accuracy of 99.3% for detection of OV (Fig. 4).

4. DISCUSSION

Cirrhosis is a chronic state with a high mortality. It represents the 5th leading cause of deaths in adult and ranks 8th in economic cost amongst the main diseases. It causes 1.3 million deaths per year world level. Cirrhosis is a heterogeneous disease that can't be managed or studied as a single entity and is categorized in two main prognostic stages: compensated and decompensated cirrhosis [5], with a median survival in the compensated stage that exceeds 12 years, while it is only 1.8 years in patients who progress to decompensation [6]. It generally goes to the decompensated stage at a rate of 5 - 7% annually [7].

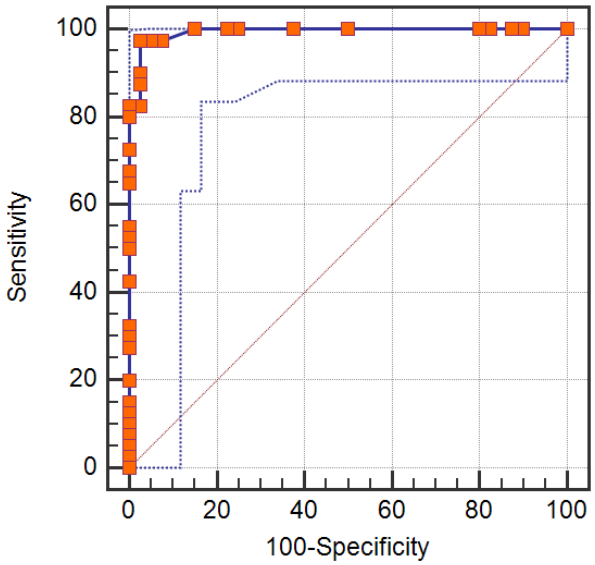

Fig. 4. ROC curve of immature platelet fraction in predicting esophageal varices

Portal hypertension (HVPG > 5 mm Hg) is the preliminary and major consequence of cirrhosis and is responsible for the most of its complications. Clinically significant portal hypertension (CSPH), defined as an HVPG ≥10 mm Hg. CSPH is linked with an increased risk of developing varices [8].

OV are portosystemic collateral veins, and consider the most common clinical consequences of portal hypertension. OV are present in around 50% of patients with cirrhosis. While OV present in only 42% of Child A patients, 72% of Child B and C patients have OV. Ruptured OV are a serious and immediate life-threatening complication of portal hypertension. It occurs at a rate of about 10%-15% per year [9].

The Baveno Consensus Workshop [10] and the American Association for the Study of Liver Diseases [8] have recommended endoscopic screening for OV in patients with cirrhosis, whatever the cause and Child class .Endoscopic surveillance should be done every 2 to 3 years in cirrhotic patients without varices, every 1-2 years in patients with small varices, and annually in the presence of decompensation [8].

Hence, there is a great need for identification of non-endoscopic, non-invasive methods that can accurately predict OV development in cirrhotic patients to recognize patients at greatest risk for bleeding and thus decrease the requirement of endoscopic screening.

Reticulated platelets are immature platelets that are produced freshly from bone marrow to peripheral circulation which can be used as a good sign for the thrombopoiesis activity. A significant raises in IPF% in cirrhotic patients especially those who develop OV as a complication of portal hypertension [11].

There was statistically significant difference as regard Clinical data (ascites, lower limb edema, jaundice and hepatic encephalopathy) among the two studied groups in our study.

This was similar to the study conducted by Nada L et al. [12] that was carried on 372 patients where cirrhotic patients with ascites were shown to have an increased risk of having OV.

There was a statistically significant difference between both studied groups regarding Child score which was higher in patients with OV than those without OV (P-value<0.001). Similar finding was reported by Cherian et al. [13] that was carried on 229 cirrhotic patients, the presence of OV was significantly connected with Child score, and that classes B/C, were significant predictors for large OV presence.

The variceal presence correlates with the severity of liver disease as The World Gastroenterology Organization Global Guidelines 2014 stated that varices present in 40% of Child A, in 85% of Child C and in 16% of hepatitis C patients with bridging fibrosis [14].

In this study the complete blood count indices had no relation to the existence of OV except the platelet count which showed inverse relationship between it and the presence of OV.

This was in agreement to what was documented by Colli A et al. [15] that found out that platelet count could be used to diagnose varices of any size with sensitivity of 0.71 and specificity of 0.80 in patients with liver cirrhosis and splenic vein thrombosis.

Thrombocytopenia may be due to thrombopoietin deficiency in advanced liver disease and the possibility of increased destruction of platelets because of hypersplenism [16].

As regard renal function tests we found no significant difference between the two groups in our study. Similar data was reported by Kraja B, et al. [17].

There was statistically significant difference between our studied groups regarding serum albumin. This result is in agreement with Hossain et al. [18] in a study which was done on 100 cirrhotic patients for assessment of hypoalbuminaemia and its association with development of OV also concluded that hypoalbuminaemia is a good marker for the presence of OV with specificity 83.8%, PPV 62.06% and NPV 80.2%.

Also agree with Salem M et al. [19] on 120 patients that found low level of serum albumin was significantly prevalent in patients with varices. Hypoalbuminaemia in cirrhosis is multifactorial and might be owing to decreased production as liver parenchyma is replaced by fibrous tissue, or increased loss through gut as portal gastropathy/enteropathy all are associated with portal hypertension.

In our study we could detect correlation between bilirubin level and INR with OV. This was in

agreement to what was documented by Gao L et al. [20]. On the other hand Masjedizadeh et al. [21] who showed no association between prothrombin time and bilirubin level with OV (with P- value 0.931 and 0.74 respectively).

As regard CRP there was significant difference between the two studied groups in our study. Similar data was reported by Mjasnikova M, et al. [22]. Also Ichikawa T et al. [23] on 154 cirrhotic patients that found a strong relation between CRP and Child score C. Elevated CRP is common in patients with advanced cirrhosis with bacterial translocation which complicates the rise in intestinal permeability in those patients. This was against the study documented by El-Marakbi A et al. [24] that found no significant relation between CRP and OV.

There was significant difference between the two groups as regards splenic longitudinal diameter. We found that the mean value of SLD to be significantly greater in patients with OV than with no EV. Splenic longitudinal diameter can be presented as a good predictor for the presence of varices.

In accordance to our result Jamil Z et al. [25]; Gunda DW et al. [26] with cutoff point: 15.2 cm; sensitivity 65.9% and specificity 65.2%. Hassan EA et al. [27] also found a significantly increase in SLD in patients with EV in comparison to patients without. They showed that a SLD ≥ 13.1 cm had 100% sensitivity and 65% specificity for the prediction of EV.

The main aim of our study was to evaluate the role of IPF as a non-invasive, simple and cheap predictor of OV, we found that there is a statistically significant difference between the two studied groups as regards immature platelet fraction with (P <0.001).

We also found cutoff value more than 12 could significantly predict OV with high sensitivity 93%, and excellent specificity 97.5%, PPV 97.6%, NPV 100%.

These results agreed with those of Rauber P et al. [11] which was conducted on 88 cirrhotic patients. The study showed inverse correlation between IPF% and platelet count as our study showed. These results are in contrast to Nomura T et al. [4] a study that observed no correlation between platelet count and IPF%.

In our study there was also a significant correlation between severity of cirrhosis as Child pugh score and IPF% also there was a significant correlation between IPF% and CRP.

5. CONCLUSIONS

IPF is elevated in cirrhotic patients with naive OV than in cirrhotic patients without varices. IPF could be used as a noninvasive, easy to measure method for detection of the presence of OV at a cutoff level of >12.

CONSENT AND ETHICAL APPROVAL

All patients had signed a written consent form and the study underwent an ethical committee assessment procedure.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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