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Assessment of Platelet Aggregation, and Fibrinolytic Activity in Egyptian Patients with Decompensated Liver Cirrhosis

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Authors' contributions

This work was carried out in collaboration between all authors. Authors FMA and GNR designed the study, performed the laboratory analysis, wrote the protocol and wrote the first draft of the manuscript. Authors FAK and ASA managed the clinical cases, analyses of the study and discussion. Authors MIS and HS managed the literature searches and revised the final manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Background: Advanced liver disease is commonly associated with complex haemostatic defects that include impaired synthesis of clotting factors and coagulation inhibitors in association with thrombocytopenia and platelets defects.
Aim of the Study: It was designed to determine whether a significant increase in circulating D-dimer levels and deterioration of platelet aggregation test may be observed in patients with liver cirrhosis complicated by ascites and bleeding tendency.
Patients and Methods: A total of 90 patients were studied and were classified into three groups. Group I included 30 patients with compensated liver disease, group II included 30 patients with decompensated liver disease without ascites and group III included 30 patients with decompensated liver cirrhosis with ascites. 30 normal healthy blood donors were considered as

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control group (IV). As well, the patients were classified into Child–Pugh class A to C. All participants were clinically evaluated, had routine laboratory investigations and assessment of platelets aggregation tests and plasma D-dimer was determined in all samples.
Results: Decreased platelet aggregation tests against various agonists such as adenosine diphosphate (ADP), epinephrine, ristocitin and collagen and elevated plasma D-dimer level showed high significant difference among the three studied groups being worse in group III (P 0.001). According to sub classification of patients to Child Pugh score decreased platelet aggregation tests and elevated plasma D-dimer revealed high significant difference between the three classes being worse in class C. (P>0.001).
Conclusion: Liver cirrhosis is implicated in alterations of platelet aggregation tests with platelet hypo-aggregability being more evident during relatively later disease stages compared with the earlier ones.

Keywords: Platelet aggregation; fibrinolytic activity; liver cirrhosis.

1. INTRODUCTION

Cirrhosis is a form of chronic liver disease (CLD) resulting from sustained liver damage from a number of causes, including viral infection. Progressive fibrosis of the normal liver architecture causes increased intrahepatic resistance and the development of portal hypertension, ultimately leading to diminished liver function and potentially life-threatening complications [1].

Patients with liver cirrhosis suffer from complex coagulation changes. There is a state of hyper-fibrinolysis in decompensated cirrhosis. Abnormal fibrinolytic activity is a major hemostatic defect in patients with liver parenchymal damage [2].

Fibrinolytic activity can be measured by plasma level of D-dimer which represents an accurate marker of fibrinolytic activity. D-dimer is formed by the factor XIII cross-linking and plasmin hydrolysis of fibrin monomer. It is considered an early diagnostic marker for thrombosis and a sensitive indicator of abnormal coagulation. D-dimer level also is an important sign of decompensation in cirrhotic patients and as a fibrin related-marker might help in diagnosis of liver cirrhosis-associated dysfunctional coagulation [3-4].

On the other hand, it was mentioned that platelets have an important role in the process of hemorrhage control. This involves primary aggregation and formation of platelet plug; secondary aggregations that increase the size of this plug, formation of blood clot [5].

It was suggested that impairment of platelet function in patients with chronic liver disease is reflected by prolonged bleeding time, impaired platelet aggregation and reduced platelet adhesiveness in those patients. Decreased aggregability has been attributed to the defective (transmembrane and intracellular) signaling, a storage pool defect and an up-regulation of the inhibitory pathways [6].

Accordingly, it is useful to understand the discrepancies in different platelet functions, to achieve better understanding of disease pattern and pathophysiology of liver disease, portal hypertension, liver fibrosis and better treatment regimens therefore can be expected. Additionally, there are limited studies correlate changes in platelet function with changes of D-dimer plasma level as marker of fibrinolytic activity in patients with decompensated liver cirrhosis. The present study aimed to assess platelet aggregation tests and D-dimer level as a predictor of bleeding or thrombosis in patients with liver cirrhosis.

2. PATIENTS AND METHODS

This study was carried out as cross-sectional analytic study. Ninety (90) patients with liver cirrhosis due to HCV viral infection and were classified into three groups: group I included thirty (30) patients with compensated liver disease, group II included thirty (30) patients with decompensated liver disease without ascites and group III included thirty (30) patients with decompensated liver cirrhosis with ascites according to certain inclusion criteria: patients with liver cirrhosis (aged 18- 70, of any sex). The diagnosis of liver cirrhosis was established on the basis of clinical, biochemical, imaging ultrasonography and/or computed tomography scanning. Decompensated cirrhosis was defined as the presence of the following 5 criteria:

hypoalbuminemia, hyperbilirubinemia, ascites, peripheral edema of non-cardiac, or renal origin and encephalopathy [7]. Exclusion criteria: Patients were excluded from the study if there was any of the following: history of bleeding diathesis; history of deep venous thrombosis or portal vein thrombosis; current use of anticoagulant therapy, vitamin K or receiving plasma expanders; any Patients with hepatocellular carcinoma or other known malignancy; patients with evidence of infection e.g. spontaneous bacterial peritonitis or urinary tract infection; refusal to participate in the study and if missing clinical and laboratory data of patients. Thirty persons were included as healthy control group and evaluated for all laboratory investigations included in the study serving as group IV. This study was approved from local research ethics committee of faculty of medicine, Suez Canal University.

All patients were clinically evaluated and abdominal ultrasonography giving an attention to hepatobiliary system. Laboratory investigations: All the following investigations were done: Complete blood count for platelet count was carried out using automated cell counters (CELL-DYN 3700, abbott diagnostics). PT, PTT & INR: to evaluate risk of bleeding; Liver function tests (ALT, AST, serum albumin, serum bilirubin) were carried out using HITACHI 912 automatic analyzer (Roche Diagnostics GmbH. Sandhofer Str. Mannheim, D-68298 Germany), for evaluation of hepatocellular injury in order to categorize patients according to the modified Child Pugh Classification; Assessment of D-dimer: Plasma D-dimer was measured by a latex-enhanced, immuno-turbidimetric test using a commercially available kit. The D-dimer concentration was expressed in µg/L and Assessment of platelet aggregation tests by Light transmission aggregometry. It measures the ability of various agonists to platelets to induce in vitro activation and platelet to platelet activation. Agonists are ADP, collagen, ristocitin, and adrenaline. These agonists interact with platelets and activate various receptors. Percent of maximum aggregation was recorded for each agonist and platelets aggregation activity were normalized and adjusted based on the platelet count [8].

2.1 Statistical Methods

The data were coded and organized. The final study results were stated using the SPSS program version 22. Results were presented through tables. Categorical data are summarized as a percentage of the group total with corresponding 95% Confidence intervals and were expressed either as frequency or mean±SD. The Chi - square test was used for qualitative variables while the independent *t* test was used for quantitative variables. Continuous Analysis of variables (ANOV) was analyzed by multiple comparisons (F-test). *P*-value of <0.05 was considered as statistically significant.

3. RESULTS

Comparison between the studied groups regarding demographic data revealed that there was no significant difference between the studied groups regarding age and sex (P value >0.05). Comparison between the studied groups regarding clinical characteristics revealed high significant difference between the three studied groups regarding bleeding tendency, beta blockers treatment, encephalopathy, liver size, spleen size and jaundice(P-value=0.001). (Table 1).

Comparison between the studied groups regarding laboratory investigations revealed significant difference between the groups regarding; platelet count, PT, PTT, platelet aggregation tests and D-dimer revealed high significant difference between the studied groups being worse in group 3 (P-value 0.001) (Table 2).

Comparison between the different groups of Child Pugh classification regarding platelet aggregation tests and D-dimer revealed high significant difference between the three classes being worse in class C. (Table 3).

Comparison between cirrhotic patients with bleeding and cirrhotic patients without bleeding regarding; platelet count, PT, INR, platelets aggregation tests with different agonists (ristocitin, ADP, collagen and epinephrine) and D-dimer, revealed high significant difference as those parameters were worse in cirrhotic patients with bleeding (Table 4).

Comparison between all the patients (90 cirrhotic patients) and control group revealed high significant differences between the two groups regarding; platelet count, PT, PTT, platelet aggregation tests and D-dimer (P-value <0.001) (Table 5).

Table 1. Comparison between groups regarding demographic & clinical characteristics

Age (Years)		Group I	Group II	Group III	Group IV	F	P-value
		40.7 ±7.8	**54±9.7**	**56.7 ±11.4**	**32 ± 7.8**	**23.2**	**P>0.05**
Sex (Male/female)		20/10	18 /12	21 /9	22/8	0.689	P>0.05
Bleeding		0 (0%)	22 (73.3%)	20 (66.7%)	-	39.6	P< 0.001
Smoking		18 (60.0%)	18 (60.0%)	16 (53.3%)	-	0.4	P>0.05
Diabetes		7 (23.3%)	11 (36.7%)	13 (43.3%)	-	2.8	P>0.05
Beta blockers drugs		0 (0%)	23 (76.7%)	29 (96.7%)	-	64	P< 0.001
Encephalopathy		0 (0%)	20 (66.7%)	7 (23.3%)	-	32.6	P< 0.001
Liver size	*Impalpable*	20(66.7%)	9 (30%)	5 (16.7%)	-	17.1	P< 0.001
	Enlarged	10 (33.3%)	21 (70%)	25 (83.3%)	-		
Spleen	*Impalpable*	24 (80%)	8 (26.7%)	7 (23.3%)	-	24.7	P< 0.001
	Enlarged	6 (20%)	22 (73.3%)	23 (76.7%)	--		
Jaundice		2 (6.7%)	20 (66.7%)	21 (70.0%)	-	30.5	P< 0.001

Table 2. Comparison between the studied groups regarding laboratory data

	Group I	Group II	Group III	Group IV	F	P-value
Platelet count x10^3/cmm	202.4±73.6	84.4±53.1	95.4± 69.4	207±20	29.3	P< 0.001
PT (second)	11.5 ±1.3	18.5±2.6	18.7±4.4	12±0.5	54.4	P< 0.001
PTT (second)	34.6 ±3.7	38.6± 5.6	37.2±8	30±2	3.3	P< 0.05
Ristocitin % of max aggregation	60±8.9	38.8± 6.2	37.9 ±6.1	80±12	90.4	P< 0.001
ADP% of max aggregation	42.6± 5.1	34.6 ±7.4	32± 7.9	75±10	19.1	P< 0.001
Collagen% of max aggregation	60.7± 8.2	41.2 ±6.6	41.3± 6	80±9	77.5	P< 0.001
Epinephrine% of max aggregation	61.5± 8.7	42.5 ±6.1	43.4± 5.2	80±13	74.4	P< 0.001
D-dimer (µg/mL)	2.1±1.02	9.6 ±3	11.7± 4.2	1.1±.2	82.8	P< 0.001

Table 3. Comparison between Child Pugh classification groups regarding D-dimer and platelet aggregation tests

	Child A (N=30)	Child B (N=29)	Child C (N=31)	F	P-value
Ristocitin% of max aggregation	60±8.9	41.3±5.9	35.1±4.7	109.8	P< 0.001
ADP% of max aggregation	42.6±5.1	37.2±7.3	29.1±5.8	35.9	P< 0.001
Collagen% of max aggregation	60.7±8.2	44.1±5.9	38.1±5.1	95.2	P< 0.001
Epinephrine% of max aggregation	61.5±8.7	45.5±5.6	40.1±4.2	88.2	P< 0.001
D-dimer(ug/ml)	2.1±1	8.1±2.3	13.3±3.1	176.6	P< 0.001

Table 4. Comparison between cirrhotic patients with bleeding and cirrhotic patients without bleeding regarding; platelet function platelet count, PT, INR and D-dimer

	Cirrhotic patients without bleeding (N=48)	Cirrhotic patients with bleeding (N=42)	T-test	P-value
Platelet count (x10^3/cmm)	182.5±71.9	64.5±43.8	9.2	P< 0.001
PT (second)	12.9±2.4	20.1±3.1	12.4	P< 0.001
INR	1.1±0.2	1.7±0.3	11.3	P< 0.001
Ristocitin%	53.6±11.1	36.4±6.1	8.9	P< 0.001
High ADP%	41.6±4.6	30.4±7.3	8.8	P< 0.001
Collagen%	55.2±9.9	39.2±6.1	9.1	P< 0.001
Epinephrine%	55.9±10.1	41.3±5.8	8.2	P< 0.001
D-dimer(µg /mL)	4.7±4.1	11.3±3.6	3.4	P< 0.001

Table 5. Comparison between all the cirrhotic patients and control regarding laboratory data

Parameters	Cirrhotic patients (N=90)	Control (N=30)	T test	P-value
Platelet count x10^3/cmm	126.7±53.6	207±20	26.3	P< 0.001
PT (second)	16.5 ±1.8	12±0.5	44.4	P< 0.001
PTT (second)	37.6 ±3.9	30±2	3.6	P< 0.05
Ristocitin % of max aggregation	45.7±5.9	80±12	87.4	P< 0.001
ADP% of max aggregation	37.6± 5.4	75±10	17.2	P< 0.001
Collagen% of max aggregation	47.7± 8.6	80±9	67.4	P< 0.001
Epinephrine% of max aggregation	49.5± 7.7	80±13	66.4	P< 0.001
D-dimer (µg/mL)	7.1±1.5	1.1±.2	52.3	P< 0.001

4. DISCUSSION

Major issues of cirrhosis include variceal bleeding, ascites, peritonitis, hepatorenal syndrome and hepatic encephalopathy [9].In the current study patients in decompensated groups (group II& group III) had higher prevalence of jaundice, encephalopathy and bleeding than patients in group I. This was in accordance with the findings of Mobin et al., 2016 [10] in a study include 76 patients with decompensated liver disease.

Current evidence is very controversial regarding the role of prothrombin time and INR in assessing the bleeding risk in liver cirrhosis [11]. The opponents thought that liver cirrhosis had a risk of both thrombotic and bleeding states [12], and that prothrombin time and INR could not globally reflect the balance between them. By contrast, the supporters believed that prothrombin time and INR not only reflected the coagulation profile, but also indicated the severity of liver dysfunction in liver diseases. Recently, Hshieh *et al.* 2015 [13] conducted a retrospective case-control study to evaluate the association of INR with bleeding risk in cirrhotic patients with esophageal varices. This is in accordance with our findings as we found that platelet aggregation, platelet count, PT, INR were worse in cirrhotic patients with bleeding.

In the current study we found that D-dimer was significantly increased in cirrhotic patients with bleeding tendency than those without bleeding. This is in agreement with Sun and his colleagues in 2017 [14] as they found a significant association between D-dimer and 5-day bleeding risk after endoscopic therapy in their research.

Transition from compensated to decompensated cirrhosis is marked by the development of complications, including ascites, jaundice, and esophageal varices (D'Amico et al.) [15]. Child scoring is based on bilirubin and albumin concentrations, the international normalized ratio (INR), and the presence and severity of ascites and hepatic encephalopathy (HE). Scores allow classification of cirrhosis as grade A, B, or C, ranked by worsening prognosis, and scores have been shown to correlate with the frequency of postoperative complications, including renal failure, HE, bleeding, infection, intractable ascites, and worsening liver failure [16].

In the current work, D dimer level was noticed to be significantly increased as the severity of liver disease increases with progression of liver cirrhosis status as determined by Child-Pugh class. This was in accordance with the previous results obtained by Dhanunjaya and his colleagues in 2013 [17] documented the same results as they found that plasma D-Dimer levels are increased significantly with severity of liver disease.

This can be explained as hyper-fibrinolysis in liver disease is said to be due to decreased clearance of tissue plasminogen activator (tPA). Tissue plasminogen activator catalyses the conversion of plasminogen to plasmin and the subsequent breakdown of fibrin clot. In health, tPA is bound to its inhibitor plasminogen activator inhibitor (PAI-1) which limits the effect of circulating tPA. High levels of tPA have been noticed in alcoholic cirrhosis and this was associated with the decreased hepatic synthesis of PAI-1, leads to activation of fibrinolysis. Chronic liver disease has increased levels of tPA due to enhanced release by the activated endothelium and/or by reduced clearance by the diseased liver (or) decreased levels of anti-plasminogen activators (PAI). This could be aggravated by the decreased synthesis of fibrinolytic inhibiting factors. This is finally manifested in the form of increased D-Dimer levels which is a measurable parameter for assessing the entire fibrinolytic system [18-20].

The rise in D-dimer level suggests increased fibrinolytic activity in our patients. The liver is strongly involved in the regulation of fibrinolysis in the circulation, because many fibrinolysis factors in blood are either synthesized or cleared by the liver. So, there is a state of hyper-fibrinolysis in decompensated cirrhosis. Abnormal fibrinolytic activity is a major factor in hemostatic defect in patients with liver damage (Leebeek and Rijken) [21].

Moreover, in our study it was noticed that D-dimer level was elevated in patients with decompensated liver disease with ascites than those without ascites. Similar results were obtained by other researchers, such as Saray et al. [4] who found that D-dimer mean values was significantly higher in patients with liver cirrhosis and ascites than in patients with liver cirrhosis with no signs of ascites ($p<0.001$). Ibrahim and his colleagues in 2011 [22] found that the mean level of plasma D-dimer in patients with liver cirrhosis and ascites (3.3 ± 2 mg/L) was statistically significantly higher than in patients with liver cirrhosis without ascites ($p<0.05$). Spadaro et al. [20] also found high D-dimer levels in 81% of patients with ascites and 39% of those without ascites.

Some authors tried to clarify the underlying mechanism of high D-dimer plasma levels in cirrhotic patients with ascites. Violi et al. in 1993 [23] and 2011 [24] proposed that hyper-fibrinolysis in cirrhotic patients might represent a state of low grade disseminated intravascular coagulation (DIC) secondary to the passage of absorbed bacterial gut material into the systemic circulation. Agarwal et al. [25] added the major role of ascites in pathogenesis of hyper-fibrinolytic state associated with liver failure. They suggested that there was exchange of some coagulation and fibrinolytic proteins between plasma and ascitic fluid. Piscaglia et al. [26] concluded that the association between high circulating D-dimer levels and ascites might be only due to advanced liver impairment with portal hypertension and bacterial translocation.

In the current study platelet function was significantly deteriorated in decompensated groups (group II& group III). This was in accordance with the findings of Ghozlan and his colleagues in 2013 [27] who stated that the platelet dysfunction and hypo-aggregability seen in liver cirrhosis have been attributed to many factors including decreased production of Thromboxane A2, Thromboxane B2, inositol-3-phosphate (IP3)-mediated cytosolic calcium increase and decreased platelet GPIb receptor expression. Additionally, storage pool defects mainly decreased ATP and serotonin levels in the dense bodies and decreased beta thromboglobulin, platelet factor-4, and P selectin levels in the a granules could limit the effect of release on the aggregation process [28].

Witters et al. [6] suggested another possible underlying mechanism of 'platelet exhaustion'. They stated that damage of platelets occur during intravascular activation when platelets are faced with the portal hyperdynamic circulation, which causes their damage with subsequent hypofunction as approved by in vitro testing. Moreover, platelet intrinsic inhibitory pathways are up-regulated in liver cirrhosis, with an increase in the two main inhibitory messengers: cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), together with a reduced transmembrane signaling in platelets of cirrhotic patients after stimulation with thrombin or collagen [28].

Additionally, Witters et al., [6] reported that there was an increase of some negative plasma factors that could delay platelet activation in patients with liver cirrhosis. Such factors include fibrinogen-degradation products (FDPs), D-dimers, nitric oxide, apolipoprotein-E (Apo-E) and bile salts.

In our study, platelet dysfunction in form of decreased percent of platelets aggregation with various agonists was found to be worse with advanced Child–Pugh stage. Ghozlan and his colleagues [27] demonstrated the presence of platelet hypofunction, reflected by the prolonged platelet function assay closure time (PFA-100 CT) in patients with Child–Pugh stage A, B and C liver cirrhosis compared with control. The prolongation in PFA-100 CT was more pronounced in patients of Child– Pugh stage B compared with those of stage A and C. However, the difference was not statistically significant. These findings were also comparable with those of previous studies, such as those performed by Pihusch et al. [29]; Hayward et al. [30], Tripodi & Mannucci [31], Patel et al. [32], and Vinholt et al. on patients with cirrhotic liver diseases with various etiologies.

5. CONCLUSION

On the basis of these findings we conclude that liver cirrhosis is implicated in alterations of

platelet function with platelet hypo-aggregability and elevated D-dimer level being more evident during later disease stages compared with the earlier ones.

CONSENT

As per international standard or university standard, patient's consent has been collected and preserved by the authors.

ETHICAL APPROVAL

This study was approved from local research ethics committee of faculty of medicine, Suez Canal University.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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