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Fibrin Monomer in Chronic HCV Cirrhotic Patients

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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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Original Research Article

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ABSTRACT

Background: Cirrhosis is a diffuse pathophysiological state of the liver that is thought to be the final stage of various liver injuries. It is characterized by chronic necroinflammatory and fibrogenetic processes, which result in the conversion of normal liver architecture into structurally abnormal nodules, dense fibrotic septa, concomitant parenchymal exaustment, and liver tissue collapse.
Aim of this Work is to study fibrin monomer in chronic HCV patients with and without portal hypertension aiming to investigate its value in these patients and if it aides in early detection of thrombus formation.
Patients and Methods: They were fifty chronic HCV cirrhotic patients with and without portal hypertension. Patients of these study were selected from Tropical and internal medicine departments and investigated at Clinical Pathology department in Tanta University hospitals, Faculty of Medicine, Tanta University during the period from July 2018 to January 2020.
Results: The individuals included in this study were comprised as: Group 1: Twenty-five healthy volunteers (matched for age and gender) were investigated as a control group. Group 2: Twenty-five diagnosed cirrhotic patients without portal hypertension. Group 3: Twenty-five diagnosed

cirrhotic patients with portal hypertension. The result of the present study was statistically analyzed, summarized and presented in tables.
Conclusion: It may be concluded that soluble fibrin monomer complex could represent a useful marker for early detection of thrombus generation in chronic HCV cirrhotic patients. It may enable us to pick up vulnerable patients in early stages to start early management.

Keywords: Hepatitis C Virus; hepatic venous pressure gradient; model for end stage liver disease; soluble fibrin monomer and soluble fibrin monomer complex.

ABBREVIATIONS

HVPG : hepatic venous pressure gradient
MELD : Model for End Stage Liver Disease
HCV : hepatitis C virus

1. INTRODUCTION

Cirrhosis is a diffuse pathophysiological state of the liver that is thought to be the final stage of various liver injuries. It is characterized by chronic inflammation, necrosis, and fibrosis, with subsequent transformation of normal liver architecture into structurally abnormal nodules, dense fibrotic septa, parenchymal exaustment, and collapse of normal liver tissue. Worldwide, alcoholic liver disease and persistent infections caused by HBV and/or HCV are the leading causes of liver cirrhosis [1]

HCV infection is a significant concern in Egypt; it is the leading cause of chronic liver disease and imposes a significant cost on both individual and governmental economies. Portal hypertension is a frequent consequence of chronic liver illness, characterized as an abnormal increase in portal venous pressure associated with increased resistance to portal blood flow. According to their anatomical location, the causes of increased portal resistance are classified as prehepatic, intrahepatic, or posthepatic [2].

Portal hypertension is thought to develop as a result of morphological changes associated with chronic liver disease that create resistance to portal inflow. Additionally, a gradual splanchnic vasodilation exacerbates the portal hypertension syndrome by increasing portal blood flow [3]. Many studies suggest that the contribution of hepatic sinusoidal endothelial dysfunction could be blamed in elevating portal pressure [4].

HCV infection is a risk factor for sinusoidal portal hypertension, which is caused by microthrombi identified as a result of the disease. Hypercoagulable condition is prevalent in chronic liver disease, both with and without portal hypertension. Portal hypertension finally results in the development of collateral circulation via the liver, defining the clinical condition of portal hypertension as a rise in the hepatic venous pressure gradient (HVPG) greater than 5 mmHg. When portal hypertension exceeds 10mmHg, problems such as portal vein thrombosis may occur. The risk is partially determined by the degree of liver disease [5,6].

Soluble fibrin monomer complex and fibrin monomer are well known markers for hypercoagulability. It results from cleavage of fibrinogen by thrombin [7]. Fibrin monomer has been found in high concentrations in hypercoagulable state, such as portal vein thrombosis and other cases as malignancy, pregnancy, ischemic stroke, acute myocardial infarction, deep venous thrombosis, atrial fibrillation, and esophageal varices [8]. Fibrin monomer has circulatory half-life 2.3h. It denotes thrombin generation in the axis of thrombus formation. So, early detection of coagulation derangement is an important step in preventing portal vein thrombosis if other risk factors can be avoided.

2. AIM OF THE WORK

The purpose of this study is to examine fibrin monomer in chronic HCV patients with and without portal hypertension to determine its use in these patients and to determine whether it aids in the early diagnosis of thrombus development.

3. PATIENTS AND METHODS

3.1 Patients

They were fifty chronic HCV cirrhotic patients with and without portal hypertension .Patients of these study were selected from Tropical and internal medicine departments and investigated at Clinical Pathology department in Tanta University hospitals during the period from July 2018 to January 2020.

Normal healthy volunteers of same age and gender served as the control group.. The individuals were classified into the following groups:-

- **Group (1)** comprised twenty-five apparently healthy volunteers. They were 16 males and 9 females with age ranged from 40-64 years.
- **Group (2)** included twenty-five (25) HCV cirrhotic patients without portal hypertension. There were 14 males and 11 females in the group, ranging in age from 44 to 69 years.
- **Group (3)** included twenty five (25) HCV cirrhotic patients with portal hypertension. They were 19 males and 6 females with age ranged from 54-67 years.

3.1.1 Inclusion criteria

- Chronic HCV cirrhotic patients with and without portal hypertension.
- Age and sex apparently healthy volunteers.

3.1.2 Exclusion criteria

The patients following will be excluded from the study:

- Patients with Disseminated Intravascular Coagulation.
- Patients with malignancy.
- Patients with Ischemic stroke.
- Patients with portal vein thrombosis.
- Patients with Atrial fibrillation.
- Patients with Acute myocardial Infarction.
- Pregnant females.
- Post-surgical patients.
- Patients with history of deep venous thrombosis.
- Patients with hepatic encephalopathy.
- Patients previously or recently treated by anticoagulants.

All patients will be subjected to the following:

- Complete history taking.
- General clinical examination.
- Abdominal ultra-sonography.

3.1.2 Lab investigations:

Hematological investigations:

1. Complete blood picture (CBC)
2. Prothrombin time bySTA®-Neoplastine® CI 5 kit by Diagnostica stago.
3. Activated partial thromboplastin time (APTT) bySTA®-PTT Automate 5 kit by Diagnostica stago.
4. Fibrinogen level by (Clauss) method STA®-Fibrinogen 5 by diagnostic stago.

5-D-dimer level (Quantitative) by STA®-Liatest® D-Di kit by diagnostic stago.

Blood chemistry:

- Liver function tests (total bilirubin – direct bilirubin – serum total protein – serum albumin – ALT-AST –Alkaline phosphatase – blood ammonia level – Gamma glutamyl transferase) by thermofissure scientific kit (turbidimetric, colorometric and kinetic)
- Hepatitis markers : -HBs Ag
  -HCV Ab by ELISA
- Alfa feto protein
- HCV PCR RNA by quantitative PCR

3.1.3 Specific investigations

Measurement of plasma fibrin monomer level by Enzyme Linked Immunosorbent Assay (ELISA) (immunoturbidimetric method).

3.2 Methods

3.2.1 Samples collection

Blood collection was performed under sterile conditions. Using a disposable sterile plastic syringe, eight milliliters of venous blood was taken from each individual.

3.2.2 Measurement of fibrin soluble monomer using ELISA technique

Plasma fibrin monomer level was determined using an Enzyme Linked Immunosorbent Assay (ELISA).

3.2.3 Statistical analysis of the data

The present study was statistically presented and analyzed utilizing the mean, standard deviation, and chi-square test in SPSS V.22.

4. RESULTS

This study was conducted in Clinical Pathology Department, Faculty of Medicine, Tanta

University. The individuals included in this study were comprised as:

- **Group 1**: Twenty-five healthy volunteers (matched for age and gender) were investigated as a control group.
- **Group 2**: Twenty five diagnosed cirrhotic patients without portal hypertension.
- **Group 3**: Twenty five diagnosed cirrhotic patients with portal hypertension.

The result of the present study was statistically analyzed, summarized and presented in tables.

Table 1 Fig. 1 showed comparison between studied groups as regards is fibrin monomer level. Fibrin monomer level ranged from 2.2 – 5.3µg/ml (mean 3.92 ± 0.98) in control group. In cirrhotic patients without portal hypertension ranged from 22 – 54µg/ml (mean 36.60 ± 9.55) and in cirrhotic patients with portal hypertension ranged from 61 – 258µg/ml (mean 110.91 ± 60.80).

There is a significant difference among the studied groups as regard fibrin monomer level (p. value= 0.001).

Table 2 Fig. 2 showed Comparison between studied groups as regards Fibrinogen level. Fibrinogen level ranged 170 – 360 mg/dl (mean 256.36 ± 58.12) in control group. In cirrhotic patients without portal hypertension ranged from 174 – 352 mg/dl (mean 242.24 ± 49.37) and in cirrhotic patients with portal hypertension ranged from150 – 232 mg/dl (mean 195.80 ± 28.09).

with portal hypertension and cirrhotic individuals without portal hypertension. (p=0.001).

There is a significant difference in fibrinogen levels between cirrhotic patients with portal hypertension and the control group (p-value =0.001).

Table 3, Fig. 3. Correlation between fibrin monomer level with another fibrinogen, d-dimer, viral load, AFP and portal vein caliber.

There was positive correlation between fibrin monomer level and each of D- dimer, AFP, viral load, and Portal vein caliber. and negative significant correlation between fibrin monomer level and fibrinogen level.

Table 1. Comparison between all studied groups as regards fibrin monomer level (µg/ml)

Fibrin monomer Conc. (µg/ml)	Group 1	Group 2	Group 3 Num=17 patients
Range	2.2 – 5.3	22 – 54	61 – 140
Mean ± SD	3.92 ± 0.98	36.60 ± 9.55	110.91 ± 60.80
f. test	59.515		
p. value	0.001*		

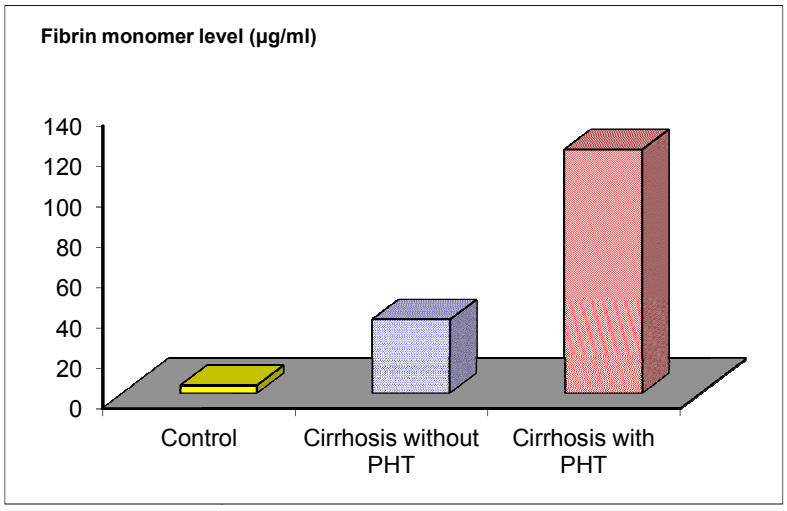

Fig. 1. Comparison between all studied groups as regards fibrin monomer level (µg/ml)

Table 2. Comparison between all studied groups as regards Fibrinogen level (mg/dl)

Fibrinogen level (mg/dl)	Group 1	Group 2	Group 3
Range	170 – 360	174 – 352	150 – 232
Mean ± SD	256.36 ± 58.12	242.24 ± 49.37	195.80 ± 28.09
f. test	11.402		
p. value	0.001*		
Group 1 & Group 2	**Group 1 & Group 3**	**Group 2 & Group 3**	
0.291	0.001*	0.001*	

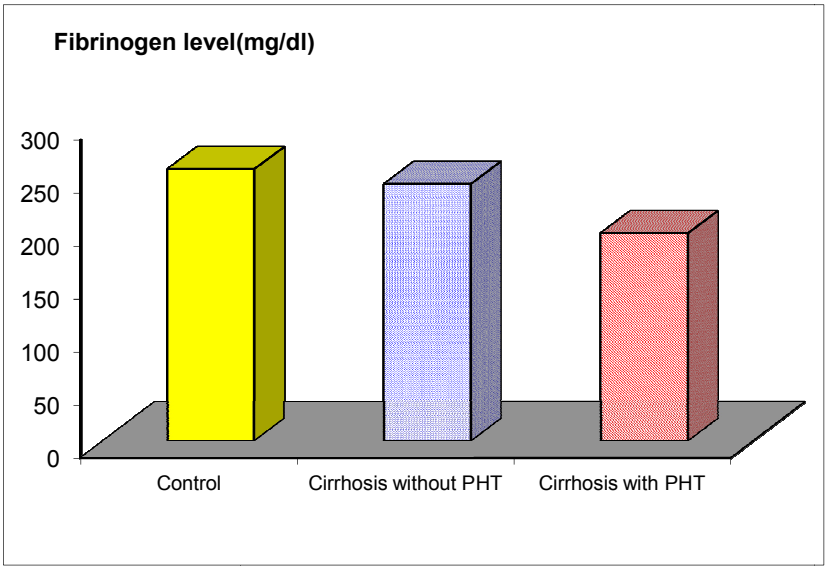

Fig. 2. Comparison between all studied groups as regards Fibrinogen level (mg/dl)

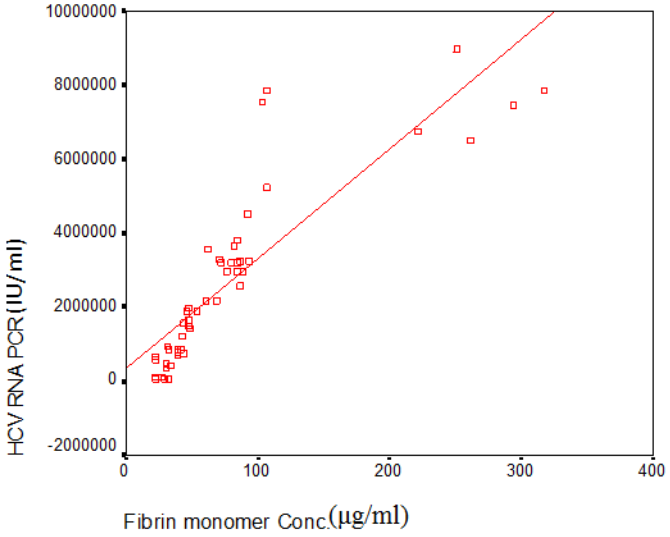

Fig. 3. Positive correlation between fibrin monomer level with viral load

Table 3. Correlation between fibrin monomer level with fibrinogen, d-dimer, viral load, AFP and portal vein caliber

	Fibrin monomer	
	r	P
Viral load	0.867	0.001*
D-Dimer	0.653	0.001*
Fibrinogen level	- 0.611	0.001*
AFP	0.868	0.001*
Portal vein caliber	0.660	0.001*

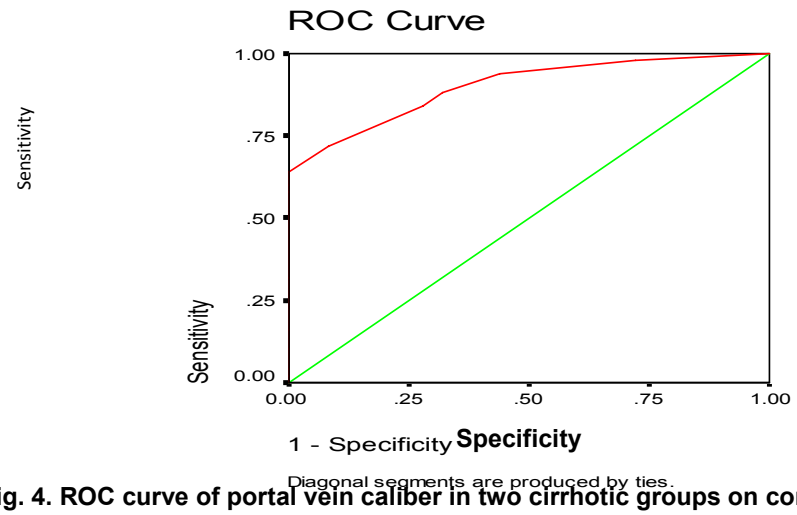

Fig. 4. ROC curve of portal vein caliber in two cirrhotic groups on comparison with control group

Table 4.ROC curve of portal vein caliber in two cirrhotic groups on comparison with control group

	Cutoff	AUC	Sensitivity	Specificity	PPV	NPV	Accuracy
Portal vein caliber (mm)	11	0.900	84	92	95	74	87

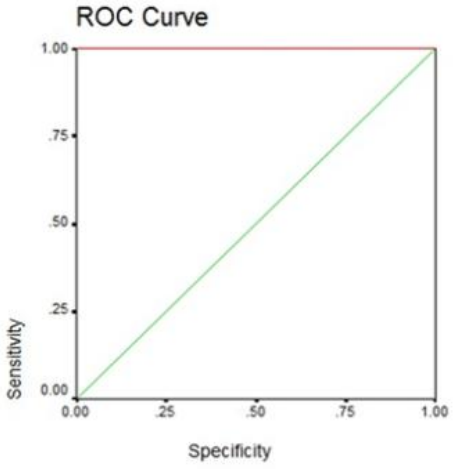

Fig. 5. ROC curve of fibrin monomer in two cirrhotic groups on comparison with control group

Table 5. ROC curve of fibrin monomer in two cirrhotic groups on comparison with control group

	Cutoff	AUC	Sensitivity	Specificity	PPV	NPV	Accuracy
Fibrin monomer	13	1.0	100	100	100	100	100

Table 4 and Fig. 4 showed ROC curve of portal vein caliber in two cirrhotic groups on comparison with control group showing the following:

Portal vein caliber cutoff was 11 mm, sensitivity 84%, specificity 92%, positive predictive value 95%, negative predictive value 74% and accuracy 87%.

Table 5 and Fig. 5 showed ROC curve of fibrin monomer in two cirrhotic groups on comparison with control group showing the following:

Fibrin monomer cutoff was 13 µg/ml, sensitivity 100%, specificity 100%, positive predictive value 100%, negative predictive value 100% and accuracy 100%.

4. DISCUSSION

Over 180 million people globally are infected with chronic hepatitis C virus (HCV). As a result, the burden of liver disease remains substantial, with HCV continuing to be a prominent cause of cirrhosis and the primary reason for liver transplantation [9].

Hypercoagulability is a significant haematological complication of cirrhosis, shown by a reduction in procoagulant factors (fibrinogen, factor II, V, X, VII, IX, XI, XII) and an increase in anticoagulant factors (protein C, protein S and antithrombin III) [10].

Soluble fibrin monomer (sFM) is a biomarker for thrombus formation in the systemic circulation. At the onset of coagulation, soluble fibrin monomers form complexes with fibrinogen, which are referred to as soluble Fibrin Monomer Complexes (SFMC) [11].

This study aimed to early predict thrombus generation in chronic HCV cirrhotic patients with and without portal hypertension by measuring plasma level of fibrin soluble monomer.

This study depends on conventional ultrasound indices (portal vein diameter and splenic size) and simple laboratory tests (WBCs, Platelet, PT,INR ,APTT, serum bilirubin, serum albumin, serum creatinine) in evaluating the stage of the chronic HCV cirrhotic patient and into HCV cirrhotic patients without portal hypertension and HCV cirrhotic patient with portal hypertension. Our investigation found a statistically significant difference in portal vein diameter (PVD) between cirrhotic and control individuals. When portal vein diameter was compared between the two sick groups, a statistically significant difference was observed. These results were in agreement with the studied one *by* Bintintan et al. [12] who stated that increasing the diameter of portal vein is positively correlated with splenomegaly and esophageal varices as a complication of portal hypertension.

This investigation established a statistically significant difference between the two cirrhotic groups in serum albumin, platelet count, prothrombin time, and bilirubin ($P<0.001$). Additionally, statistically significant differences were seen between the two cirrhotic groups and the control group. These results were in agreement with the studies by Muhammad et al. [13] as regarding the same parameters respectively.

Thrombocytopenia is more prevalent in individuals with HCV infection due to a multitude of factors, one of which is direct bone marrow suppression [14]. Another explanation is that congestive splenomegaly develops as a result of portal hypertension, which results in sequestered thrombocytopenia. Additionally, reduced thrombopoietin production in the liver (a crucial component in the development of thrombocytopenia in cirrhosis) [15].

Regarding serum creatinine levels, the study indicated that the difference between cirrhotic patients and the control group was statistically significant. There was also a statistically significant difference in serum creatinine between the two groups .These results were in agreement with the study by Wong et al. [16] who reported that at least 20% of patients admitted to the hospital with decompensated cirrhosis develop renal dysfunction with high serum creatinine level that was associated with poor prognosis in this population .This is due to progressive disease process, So creatinine level

has an important role in determination and stratification of cirrhotic patients for liver transplantation through estimating (MELD) score.
.
Results were obtained by other researchers, such as Saray et al. [17] 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 ($p<0.001$).

The rise in D-dimer level documents increased fibrinolytic activity in our patients. The liver plays a critical role in the control of fibrinolysis in the circulation, since the liver synthesizes or eliminates a large number of fibrinolytic components found in blood. Thus, in decompensated cirrhosis, there is a condition of hyperfibrinolysis. In individuals with liver injury, abnormal fibrinolytic activity is a significant component in hemostatic dysfunction [18].

Regarding the level of soluble fibrin monomer, the current investigation established a statistically significant difference between the two cirrhotic groups. Additionally, statistical significance was seen between the two cirrhotic groups and the control group. This results were in agreement with Mirshashi et al. [19] who reported that assessment of plasma fibrin monomer together with D-dimer in HCV cirrhotic patients are helpful tool for early detection of venous thromboembolism .

Another study by Khan [20] agreed with the present study as he reported that with progressive increase in portal pressure, the portal venous flow is markedly reducing and this reduction markedly correlated with parenchymal affection resulting in significant increase in fibrin monomer, ALT, total bilirubin and INR.

Fibrinogen levels may remain within the normal range or may decrease in advanced cirrhosis. [21]. Since the fibrinogen level increases in inflammatory states and cirrhosis may be accompanied by inflammation, The final concentration of fibrinogen is the consequence of an equilibrium between two antagonistic processes (inflammation and a diminished capacity of the liver to synthesize fibrinogen). [22]

A study by Mostafa et al. [23] agreed with the present study as regarding the diagnostic performance of fibrin monomer as this study showed that plasma fibrin monomer has high sensitivity and specificity in detecting early thrombus formation in HCV cirrhotic patients.

The increased sensitivity and specificity of plasma fibrin monomer may be explained by the fact that fibrin monomer cannot originate from inflammatory sites due to its large molecular weight; hence, the presence of FM in plasma serves as a specific marker of intravascular coagulation initiation [24].

However, claimed that estimation of fibrin monomer levels could be a tool to monitor or modulate anticoagulant therapy in patients with suspected venous thromboembolism [25].

5. CONCLUSION

It may be concluded that soluble fibrin monomer complex could represent a useful marker for early detection of thrombus generation inchronic HCV cirrhotic patients. It may enable us to pick up vulnerable patients in early stages to start early management.

6. LIMITATIONS

A major limitation of the present study is the small sample size. Thus, further larger studies are required to increase the sensitivity and specificity of the findings.

ETHICAL APPROVAL

The study was authorized by the ethics committee of the faculty of medicine at Tanta University.

CONSENT

All participants provided written informed permission.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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