

Fibrin Monomer in Chronic HCV Cirrhotic Patients

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 characterised by chronic necroinflammatory and fibrogenetic processes, which result in the conversion of normal liver architecture into structurally abnormal nodules, dense fibrotic septa, concomitant parenchymal exhaustion, 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 aids 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 were 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.

Key words Hepatitis C Virus, hepatic venous pressure gradient, Model for End Stage Liver Disease, Soluble fibrin monomer and soluble Fibrin Monomer Complex

Introduction

Cirrhosis is a diffuse pathophysiological state of the liver that is thought to be the final stage of various liver injuries. It is characterised by chronic inflammation, necrosis, and fibrosis, with subsequent transformation of normal liver architecture into structurally abnormal nodules, dense fibrotic septa, parenchymal exhaustion, 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, characterised 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

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.

Patients and Methods

I- 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 study was authorised by the ethics committee of the faculty of medicine at Tanta University, and all participants provided written informed permission. 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.

Inclusion criteria:

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

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.

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

Table (1) figure (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 (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*		

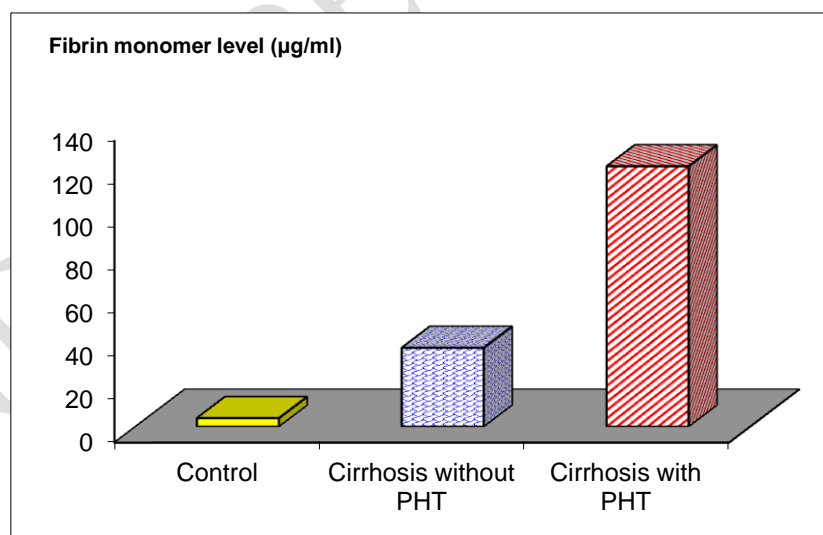


Figure (1): Comparison between all studied groups as regards fibrin monomer level (µg/ml).

Table (2) figure (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 from 150 – 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 (pvalue =0.001).

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 \pm SD	256.36 \pm 58.12	242.24 \pm 49.37	195.80 \pm 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*	

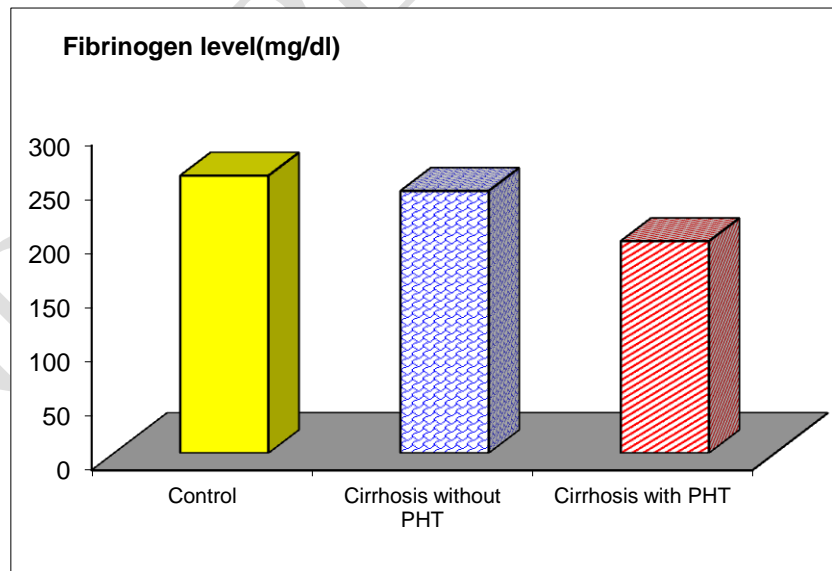


Figure 2): Comparison between all studied groups as regards Fibrinogen level (mg/dl).

Table (3) figure (3):Correlation between fibrin monomer level with other 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.

UNDER PEER REVIEW

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*

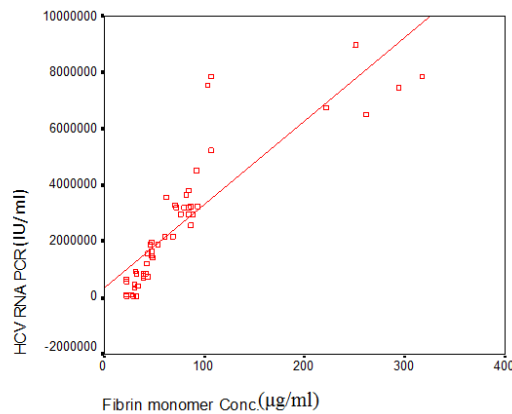


Figure (3) positive correlation between fibrin monomer level with viral load.

Table (4)and Figure (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%.

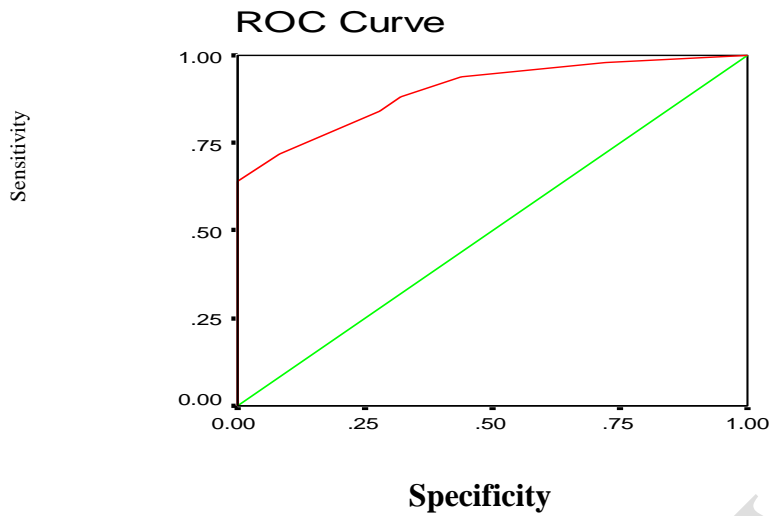


Figure (4) ROC curve of portal vein caliber in two cirrhotic groups on comparison with control group

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

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

Fibrin monomer cutoff was 13 $\mu\text{g/ml}$, sensitivity 100 % , specificity 100 % ,positive predictive value 100%, negative predictive value 100% and accuracy 100%.

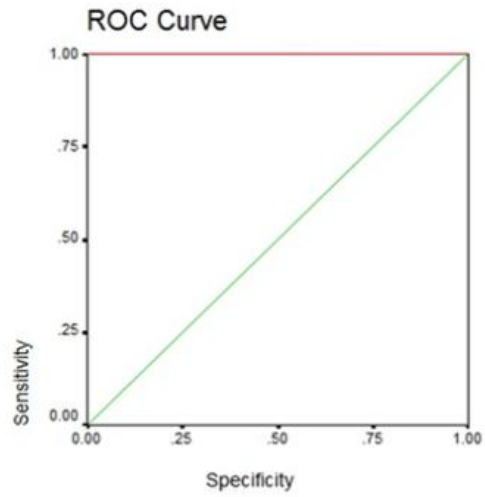


Figure (5) ROC curve of fibrin monomer in two cirrhotic groups on comparison with control group.

UNDER PEER REVIEW

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

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 studies done by *Bintintan et al.*, (12) who stated that increasing the diameter of portal vein is positively correlated with splenomegaly and oesophageal 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 **Sarayet 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 synthesises 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 reduces 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 synthesise 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).

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.

Abbreviations

(HVPG): hepatic venous pressure gradient

(MELD): Model for End Stage Liver Disease

(HCV) : hepatitis C virus

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. 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.

References

1. **Grace JA and Angus PW (2013)** :Hepatopulmonary syndrome: update on recent advances in pathophysiology, investigation, and treatment. *J GastroenterolHepatol*; 28(2): 213–219.
2. **Gower E , Estes C, Blach S , et al ., (2014)**:Global epidemiology and genotype distribution of the hepatitis C virus infection. *J Hepatol.* ;61 (1) : S45-S57.

3. **Bosch J, Abraldes JG, Fernández M, et al.,(2010):** Hepatic endothelial dysfunction and abnormal angiogenesis: New targets in the treatment of portal hypertension. *J Hepatol.* 53 (3) : 558-567.
4. **Bosch J, Groszmann R J, and Shah V ,(2015):** Evolution in the understanding of the pathophysiological basis of portal hypertension: How changes in paradigm are leading to successful new treatments. *J Hepatol* 62 (1) : S121-S130.
5. **Plessier A, Darwish -Murad S , Hernandez-Guerra M , et al .,(2010):** Acute portal vein thrombosis unrelated to cirrhosis: a prospective multicenter follow-up study. *Hepatology* ; 51 (1) : 210-218.
6. **Berzigotti A, Seijo S, Reverter E ,et al., (2013) :** Assessing portal hypertension in liver diseases. *Expert Rev GastroenterolHepatol*; 7 (2) :141–155
7. **Shimomura M , Kochi M , Hinoi T , et al ., (2016) :**Clinical significance of pharmacological prophylaxis based on the original classification of venous thromboembolism after lower abdominal surgery. *Hiroshima J Med Sci* ;65 (3-4) :53–59.
8. **Jiang Y, J Li , Zhang WH , et al.,(2015) :**Risk factors for deep vein thrombosis after orthopedic surgery and the diagnostic value of D-Dimer .*Ann Vasc surg.* ;29 (4) : 675-681.
9. **Kim WR, Stock PG , Smith JM, et al ., (2013):**Annual Data Report liver. *Am J Transplant* ; 13(Suppl. 1): 73– 102.
10. **Chaireti R , Rajani R , Bergquist A, et al ., (2014):** Increased thrombin generation in splanchnic vein thrombosis is related to the presence of liver cirrhosis and not to the thrombotic event. *Thromb Res*;134 (2):455-461.
11. **Litvinov RI and Weisel JW (2016):**What is the biological and clinical relevance of fibrin. *SeminThrombHemost.*; 42(4): 333 – 343 .
12. **Bintintan A , Chira RI , and Mircea PA , (2013):** Non-invasive ultrasound based diagnosis and staging of oesophageal varices in liver cirrhosis. *Med Ultrason*; 15 (2) :116–124.
13. **Muhammad SK , Shaikh MA, Shaikh BA, et al ., (2012):**Sensitivity, specificity and predictive values of noninvasive markers of oesophageal varices in cirrhosis of liver. *Asian J Med Res*; 1:98–102.
14. **WangCS , Yao WJ ,Wang ST,et al., (2004):** Strong association of hepatitis C virus (HCV) infection and thrombocytopenia: implications from a survey of a community with hyperendemic HCV infection. *Clin Infect Dis* ;39(6):790–796.
15. **Giannini E, Botta F , Borro P , et al ., (2003):** Relationship between thrombopoietin serum levels and liver function in patients with chronic liver disease related to hepatitis C virus infection. *Am J Gastroenterol* ;98(11): 2516–2520.
16. **Wong F , O` leary JG , Reddy KR ,et al ., (2017):** Acute kidney injury in cirrhosis: Baseline serum creatinine predicts patient outcomes. *Am J Gastroenterol* ; 112(7):1103-1110 .
17. **SarayA, Mesihovic R, Gornjakovic S ,et al ., (2012):**Association between high D dimer plasma levels and ascites in patients with liver cirrhosis. *Med Arh* ; 66(6):372-374 .

18. **Leebeek FWG and Rijken DC (2015):**The fibrinolytic status in liver diseases. *SeminThrombHemost.* ;41 (5) :474–480.
19. **Mirshahi S , Soria C , Kouchakji B , et al ., (2014):** New combinational assay using soluble fibrin monomer and D-dimer determinations; a promising strategy for identifying patients with suspected venous thromboembolism. *PLoS ONE*;9 (3) :e92379.
20. **Khan AN (2017) :**Portal hypertension imaging medicine *Medscape*;43 (2): 117-123
- 21-Zermatten MG , Fraga M , Moradpour D ,et al ., (2020):**Hemostatic Alterations in Patients With Cirrhosis: From Primary Hemostasis to Fibrinolysis. *Hepatology* ;71: 6
- 22-Saner FH, Gieseler RK ,Aktz H, et al ., (2013) :**Balance of bleeding and thrombosis in end-stage liver disease and liver transplantation . *Digestion* ; 88 (3) :135–144.
21. **Mostafa EF, Ismael WA, El Hawary A, et al ., (2018):**Hepatic microcirculatory thrombosis in acute-on-chronic hepatic failure. *Egypt J Intern Med*;30 (2) :83-89 .
22. **Hetland O, Knudsen A, Dickstein K, et al ., (2002):** Characteristics and prognostic impact of plasma fibrin monomer (soluble fibrin) in patients with coronary artery disease. *Blood Coagul Fibrinolysis*; 13 (4) :301–308.
- 23-Mirshahi S , Soria C , Kouchakji B , et al ., (2014):** New combinational assay using soluble fibrin monomer and D-dimer determinations; a promising strategy for identifying patients with suspected venous thromboembolism. *PLoS ONE*;9 (3) :e92379.