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USE OF SERUM SOLUBLE UROKINASE PLASMINOGEN ACTIVATOR RECEPTOR TO IDENTIFY SEVERITY OF LIVER FIBROSIS AND ACTIVITY IN CHRONIC VIRAL HEPATITIS C PATIENTS

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Abstract

Background: identification of individuals with severe liver fibrosis among patients with chronic liver disease is of major importance when evaluating prognosis, potential risk for complications, and when deciding treatment strategies. Attempts to find reliable noninvasive markers of liver fibrosis are frequent to avoid the complications of liver biopsy. High serum concentrations of soluble urokinase plasminogen activator receptor (suPAR) are suggested to be involved in inflammation, tissue remodeling, and cancer metastasis. **Objectives**: To evaluate serum (suPAR) as a noninvasive biomarker to detect severity of liver fibrosis and activity in patients with chronic C hepatitis infection. **Patients and Methods**: 40 patients with chronic hepatitis (C) viral infection prior to treatment with antiviral combination therapy (Pegylated Interferon, Ribavirin and Sofosbuvir) were enrolled in the study.All patients were subjected to liver biopsy with assessment of serum(suPAR) levels . **Result**: There was significant rise in suPAR level in F4 (15.3±0.3 ng/ml) compared to F3 (6.2±1.1 ng/ml) , F2 (4.0±1 ng/ml) and F1 (1.1±0.2 ng/ml) (P< 0.001).Also there was a significant rise in (suPAR) level in A2 (6.3±4.5 ng/ml) compared to A1 (1.1±0.2 ng/ml) (P< 0.001).There was a significant positive correlation between (suPAR) level with the stages of liver fibrosis(r=0.921, P< 0.001) and AFP (r=0.383, P< 0.018).On constructing receiver operating characteristics curve(ROC) for prediction of grade of activity, the cut-off value was ≥ 3.0 ng/mL can differentiate between moderate activity (A≥2) and mild activity(A< 2). For prediction of different stages of liver fibrosis , it was found that cut-off value of (suPAR) for prediction of significant fibrosis F≥2 was ≥ 2.0 ng/ml, advanced fibrosis F≥ 3 was ≥ 5.0 ng/ml, and of cirrhosis (F=4)was ≥12 ng/ml. **Conclusion**: Serum levels suPAR can predict severity of liver fibrosis and activity in patients with chronic HCV infection

Introduction

About 3–4 million people are infected per year, and more than 350,000 people die yearly from hepatitis C-related diseases. During 2010 it is estimated that 16,000 people died from acute infections while 196,000 deaths occurred from liver cancer secondary to the infection(1).After penetrating in the host HCV gives rise to an acute infection which becomes chronic in about 70% of infected people(2).About 80% of those exposed to the virus develop a chronic infection; which is defined as the presence of detectable viral replication for at least six months(3).Fatty changes to the liver occur in about half of those infected and are usually present before cirrhosis develops(4). Usually (80% of the time) this change affects less than a third of the liver (5). Worldwide hepatitis C is the cause of 27% of cirrhosis cases and 25% of hepatocellular carcinoma (6) and about 10–30% of those infected develop cirrhosis over 30 years(7).

Liver biopsies are used to determine the degree of liver damage present; however, there are risks from the procedure. The typical changes seen are lymphocytes within the parenchyma, lymphoid follicles in portal triad, and changes to the bile ducts (8).In recent years, interest in identifying and describing liver fibrosis by using non-invasive surrogate markers has been on the rise, which offers an attractive, cost effective alternative to liver biopsy for both patients and clinicians. Moreover, measurements may be performed repeatedly, thus, allowing for a dynamic monitoring of fibrosis (9).

Biomarkers of fibrosis are commonly divided into direct and indirect markers. Direct markers are fragments of the liver matrix components produced by hepatic stellate cells (HSC) during the process of extracellular matrix (ECM) remodeling. Indirect markers include molecules released into the blood due to liver inflammation, molecules synthesized/regulated or excreted by the liver, and markers of processes commonly disrupted due to liver function impairment, such as insulin resistance(10).From a pathophysiological point of view liver fibrosis is the result of an ongoing inflammatory process and an imbalance between the production of extracellular matrix and its degradation (11).Notably, the importance of coagulation pathways has been appreciated in the development of liver fibrosis and cirrhosis. In contrast, no systematic studies have focused on specific fibrinolytic/proteolytic aspects(12).

The urokinase plasminogen activator receptor (uPAR) is a glycosylphosphoinositol-anchored protein which is expressed on various cell types including inflammatory cells for example monocytes and granulocytes, connective-tissue cells, and epithelial cells (13). In addition to the membrane-anchored form, uPAR is released from the plasma membrane by cleavage of the glycosylphosphoinositol anchor and can be found as a soluble molecule in the serum termed suPAR(14).Although suPAR has been suggested to promote fibrinolysis under certain conditions in vitro, later studies showed that it inhibits fibrinolysis under physiological conditions (15). In humans, increased expression of uPAR on the cell surface has been demonstrated during several infectious diseases, inflammatory disorders, and carcinogenesis (14). Activation of the proenzyme plasminogen by tissue-type plasminogen activator or uPA leads to the generation of plasmin, a serine protease that degrades fibrin and other extracellular matrix constituents (16).

Patients And Methods

Study design

Cross-section study conducted on 40 naive patients with chronic hepatitis (C) viral infection, with age and sex matched prior to treatment with antiviral combination therapy (Pegylated Interferon, Ribavirin and Sofosbuvir) attending to internal medicine & Hepatology outpatient clinics of Ain Shams University Hospitals and Mostafa Kamel Military Hospital, from December 2014 to May 2015.Participants were subjected to U/S guided liver biopsy and was assessed histopathologicaly by Metavir score system which was used to stage liver fibrosis (F0-F4) that was scored on a five point scale (F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with few septa; F3, portal fibrosis with numerous septa; F4, cirrhosis). The grade of activity was scaled on (A0 to A3) A0;no activity, A1; mild activity, A2; moderate activity and A3;severe activity (17).

According to histopathological assessment of liver biopsy, patients were classified into different categories in order to evaluate different cut-off values as follows: $F<2$ was considered as insignificant fibrosis, $F\geq 2$ significant fibrosis, $F\geq 3$ advanced fibrosis and $F=4$ cirrhosis, $A<2$ mild activity and $A\geq 2$ moderate activity.

Diagnosis of chronic HCV infection and degree of liver fibrosis

The diagnosis of chronic hepatitis C infection and liver fibrosis was based on clinical features, laboratory test, Hepatitis C virus Antibody (HCVAb) by enzyme linked immunosorbent assay (ELISA), quantitation of HCV RNA by polymerase chain reaction (PCR), diagnostic imaging and presence of chronic hepatitis in liver biopsy, which determines grade of activity and stage of fibrosis according to Metavir score system.A written informed consent was obtained from all patients and the approval was taken from the medical ethical committee of Ain Shams University Hospitals.

Patients with chronic viral hepatitis rather than virus (C), Co infection with hepatitis (B), Autoimmune hepatitis, Wilson's disease, Haemochromatosis, Bilharziasis, history of alcohol consumption (>80 g/day for >5 years), patients with previous treatment with Antiviral therapy, Hepatocellular carcinoma (HCC), decompensated liver cirrhosis

(Child-Pugh class B, C), Thrombocytopenia (platelet count <100×103/mm3), patients receiving hepatotoxic drugs, Body mass index (BMI) ≥30, Diabetes Mellitus and pregnant females were all excluded from the study.

Tools of the study

All patients were subjected to the following:

1. Full medical history and clinical examination.
2. Laboratory investigations including: complete blood count, liver profile (Alanine Transaminase (ALT), Aspartate Aminotransferase (AST), Total billirubin, serum Albumin, Prothrombin concentration (Pc)) Renal profile (Serum Creatinine and Blood Urea Nitrogen (BUN)), serum Anti-Nuclear Antibody (ANA) and Anti-Smooth Muscle Antibody (ASMA), serum Ferritin, serum Ceruloplasmin, Bilharzial haemagglutin. Hepatitis Viral markers: Hepatitis B virus Surface Antigen (HBsAg), HBcoreAb by ELISA, Hepatitis C virus Antibody (HCV Ab) by ELISA, HCV RNA by quantitative polymerase chain reaction (PCR) and Serum Alpha fetoprotein were done. Measurement of serum soluble urokinase plasminogen activator receptor (suPAR) level as follows: 5-mL sample of peripheral blood was taken from each patient one hour before performing liver biopsy and anticoagulated by ethylene diaminetetraacetic acid (EDTA). (suPAR) was assayed using commercially available Quantikine® ELISA kit, according to the manufacturer instructions (R&D systems, DosToo, Minneopolis, MN, USA) which has the minimum detectable dose of (suPAR) ranging from 0.2 to 20 ng/ml.by quantitative sandwich enzyme immunoassay. In healthy adults, the median value of suPAR has been cited as 0.8ng/ml (18).
3. Pelviabdominal Ultrasonography equipment: Hitachi, EUB-5500. Measurements were performed after overnight fasting and the patient in supine position with emphasis on: liver size, liver echogenicity, splenic bi-polar diameter (longest axis), portal vein diameter (mm) and patency. Presence of ascites. Criteria suggestive of chronic liver disease and cirrhosis include: increased liver echogenicity, irregular liver margins, attenuation of intrahepatic portal and hepatic veins, presence of periportal thickening, relative enlargement of caudate lobe and atrophy of right lobe (ratio of caudate/right lobe in cirrhosis >0.65) (19).
4. Liver biopsy: Ultrasonography-guided liver biopsy was done for chronic hepatitis C patients only. Liver biopsies were performed using disposable semiautomatic 18- gauge true cut needle. The core biopsies were not less than 25 mm in length and contained at least 8 portal tracts and were routinely stained with hematoxylin-eosin stain. The histological features were analyzed according to Metavir score.

Statistical methodology

The collected data were coded, tabulated, and statistically analyzed using IBM SPSS statistics (Statistical Package for Social Sciences) software version 22.0, IBM Corp., Chicago, USA, 2013.Data were expressed as Mean ± SD for quantitative parametric measures and both number and percentage for categoral data. Student t-test was used for comparison between two independent mean groups for parametric data, whereas Wilcoxon Rank Sum test was used for comparison between two independent groups for non parametric data. ANOVA test for analysis of variation between more than two groups. Followed by post hoc Tukey test to find homogenous groups. Ranked Pearson correlation test was used to study the possible association between each two variables among each group, while Chi-square test was used to study the association between each 2 variables, linear regression analysis was used to detect independent effect of different parameters in prediction of outcome. The probability value was expresses as; P value <0.05-->significant, P< 0.01-->highly significant, P value > 0.05-->non significant. Diagnostic validity test was used to show sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy of the test. The ROC (receiver operating characteristics) curve was constructed to obtain the most sensitive and specific cutoff value for each technique and to evaluate the most discriminating markers between the compared groups, of which are under the curve (AUC) could be calculated.

Results

The study was conducted on 40 naive patients with chronic HCV infection, (24 males and 16 females),their age ranged from (21-58 years) with mean of (46 ± 9.8 years).

Table (1): Laboratory data of studied patients (N:40).

Lab	Mean±SD
Hb (gm/dL)	12.8±1.0
WBCs (x10^3/mL)	5.5±1.4
Platelets (x10^3/mL)	197.2±59.6
Pc %	88.8±8.6
Creatinine (mg/dL)	0.85±0.18
BUN (mg/dL)	14.5±3.3
Albumin (gm/dL)	3.8±0.4
AST (IU/L)	49.8±32.2
ALT (IU/L)	51.7±49.6
T Bilirubin (mg/dL)	0.8±0.5
D Bilirubin (mg/dL)	0.3±0.2
AFP (ng/mL)	5.8±5.7
suPAR (ng/mL)	5.5±4.5
HCV RNA (x10^3/mL)	1716.7±2724.8

AST (Aspartate Aminotransferase), ALT (Alanine Transaminase), AFP (Alpha Fetoprotein), Pc (Prothrombin concentration), BUN (Blood Urea Nitrogen), Hb (Haemoglobin), WBC (White Blood Count) suPAR (soluble Urokinase plasminogen Activator Receptor).

Regarding grade of activity (A);6 patients (15%) showed mild activity (A1) and 34 patients (85%) showed moderate activity (A2),where as regarding stage of fibrosis (F); 8 patients (20%) showed (F1), 19 patients (47.5%) showed (F2), 7 patients (17.5%) showed (F3) and 6 patients (15%) showed (F4),while regarding suPAR level, significant rise was recorded; in F4 (15.3±0.3 ng/ml) compared to F3 (6.2±1.1 ng/ml), F2 (4.0±1.0 ng/ml) and F1 (1.1±0.2 ng/ml) with high statistical significant difference (t-test value=378.87, P< 0.001)**Table(2).**Also there was a significant rise in suPAR level in A2 (6.3±4.5 ng/ml) compared to A1(1.1±0.2 ng/ml) with high statistical significant difference (t-test value=2.8,P<0.001) **Figure(1).**

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Table (2): Comparison between stages of fibrosis regarding suPAR (ng/mL).

Stage	N	Mean±SD	^P	#Homognous groups
F1	8	1.1±0.2	**<0.001***	A
F2	19	4.0±1.0		B
F3	7	6.2±1.1		C
F4	6	15.3±0.3		D

^ANOVA t-test, *Significant, #Homomgenous groups by post hoc Tukey test.

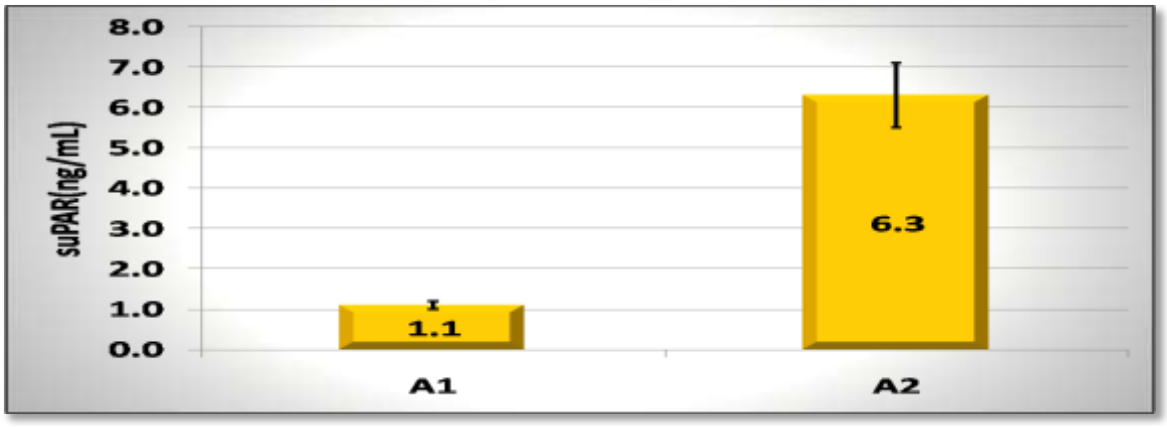

Figure (1): Comparison between grades of activities regarding suPAR level(ng/mL).

Correlating suPAR, with patients characteristics and laboratory data in different grades of activity and stages of fibrosis proved to be non significant **Tables(3,4).**

Table (3): Correlation between suPAR and patients characteristic in different grades of activity.

Variables	A1		A2	
	^r	P	^r	P
Age	-0.114	0.536	-0.114	0.536
Hb	-0.126	0.490	-0.126	0.490
WBCs	0.312	0.082	0.312	0.082
Platelets	0.263	0.146	0.263	0.146
Pc	0.081	0.661	0.081	0.661
Creatinine	0.126	0.492	0.126	0.492
BUN	-0.050	0.786	-0.050	0.786
Albumin	-0.223	0.219	-0.223	0.219
AST	0.061	0.740	0.061	0.740
ALT	-0.040	0.828	-0.040	0.828
T.Bil	-0.018	0.923	-0.018	0.923
D.Bil	-0.142	0.440	-0.142	0.440
AFP	0.273	0.131	0.273	0.131
HCV RNA	-0.217	0.232	-0.217	0.232

^Partial correlation test (controlled for fibrosis stage).

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Table (4): Correlation between suPAR, patients characteristic and laboratory data in different stages of fibrosis

		#F1	#F2	#F3	#F4
Age	**R**	0.178	-0.212	-0.189	0.392
	P	0.674	0.383	0.686	0.442
Hb	**R**	0.449	0.085	-0.112	-0.170
	P	0.264	0.729	0.811	0.748
WBCs	**R**	0.427	0.121	0.494	-0.383
	P	0.291	0.621	0.260	0.453
Platelets	**R**	-0.217	-0.146	-0.021	0.513
	P	0.606	0.550	0.964	0.298
Pc	**R**	0.088	0.433	-0.038	0.115
	P	0.836	0.064	0.935	0.828
Creatinine	**R**	-0.205	-0.109	0.329	0.580
	P	0.627	0.668	0.471	0.228
BUN	**R**	-0.086	-0.096	0.334	-0.186
	P	0.839	0.697	0.465	0.725
Albumin	**R**	0.152	-0.116	-0.740	0.258
	P	0.719	0.637	0.057	0.621
AST	**R**	-0.173	-0.025	-0.158	0.118
	P	0.683	0.919	0.736	0.823
ALT	**R**	0.441	0.085	-0.335	0.158
	P	0.275	0.729	0.462	0.765
T.Bil	**R**	0.395	0.006	-0.039	-0.314
	P	0.333	0.982	0.935	0.544
D.Bil	**R**	0.172	-0.136	-0.151	0.141
	P	0.684	0.578	0.746	0.790
AFP	**R**	0.230	-0.291	0.562	-0.473
	P	0.583	0.226	0.189	0.344
HCV RNA	**R**	-0.307	-0.427	0.318	-0.241
	P	0.460	0.068	0.487	0.646

#Pearson correlation *Significant.

On applying multivariate analysis of different parameters with suPAR there was a significant correlation between serum suPAR levels and AFP(r=0.383,P< 0.018)**Table(5),Figure(2)**,grade of activity (t-test value=2.8, P< 0.001) and stage of fibrosis (r=0.921, P< 0.001) detected by METAVIR score system **Figure(3).**

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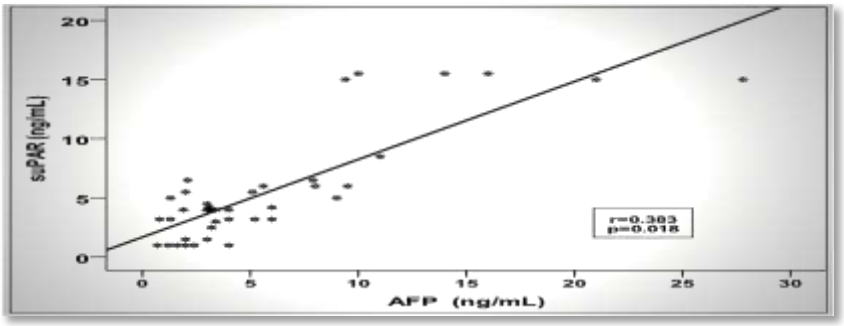

Figure (2): Correlation between suPAR and AFP in studied patients.

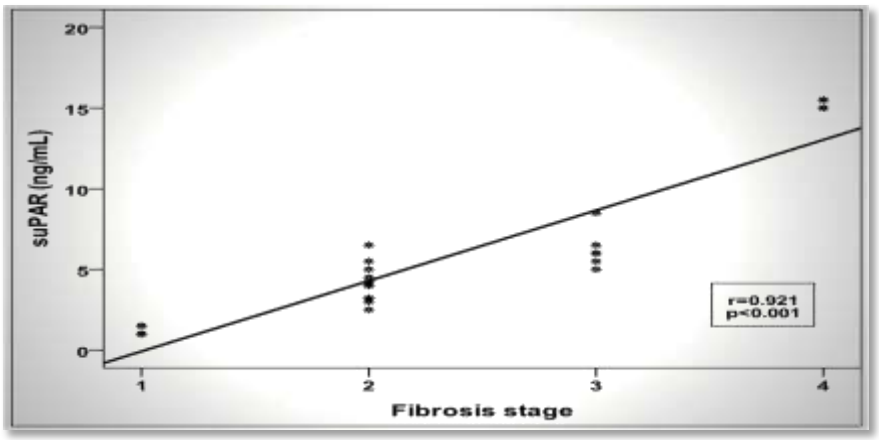

Figure (3): Correlation between stages of fibrosis and suPAR.

Table (5): Correlation between suPAR and different parameter in studied patients.

	^r	P
Age	-0.089	0.594
Hb	-0.164	0.326
WBCs	0.146	0.381
Platelets	0.288	0.080
Pc	0.103	0.540
Creatinine	0.034	0.839
BUN	0.026	0.877
Albumin	-0.073	0.658
AST	0.106	0.526
ALT	-0.039	0.814
T.Bil	0.040	0.814
D.Bil	-0.080	0.633
AFP	0.383	**0.018***
HCV RNA	0.275	0.090

Using multivariate linear regression analysis of different parameters for elevated suPAR, the stage of fibrosis was the most and only independent factor associated with rise of suPAR **Table(6).**

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Table (6): Linear regression model for factors affecting suPAR.

Factor	B	SE	P	95% CI
Stage of fibrosis	2.700	0.158	**<0.001***	2.380–3.020

β: Regression coefficient, SE: Standard error, *Significant, CI: Confidence interval.

Using ROC analysis for prediction of different stages of fibrosis and grades of activity; the area under the curve(AUROC)for suPAR as a predictor of significant hepatic fibrosis F≥ 2 was (1), with a cut off value of ≥2.0ng/ml giving a sensitivity of (100%), specificity of (100%), positive predictive value (PPV) of (100%), negative predictive value (NPV) of (100%) and diagnostic accuracy (DA)of (100%) **Figure(4)**, while that of advanced hepatic fibrosis F≥ 3 was (0.973), with a cutoff value of ≥5.0 ng/ml, giving a sensitivity of (100%), specificity of (85.2%), PPV of (63.6%), NPV of (100%), and DA of (88.2%) **Figure(5)**. The AUROC for suPAR as a predictor of cirrhosis F=4 was (1), with a cut-off value of ≥12.0 ng/ml, giving a sensitivity of 100%, specificity of (100%), (PPV) of (100%), (NPV) of (100%) and (DA)(100%)**Figure(6).**On the other hand the AUROC for suPAR as a predictor of moderate activity A≥2 was (0.980), with a cut off value of ≥3.0ng/ml giving a sensitivity of (94.1%), specificity of (100%), PPV of (100%), NPV of (75%), and DA of (95%).

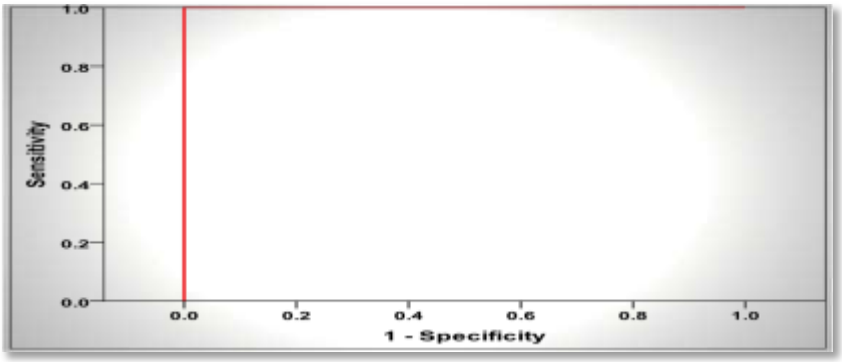

Figure (4): ROC curve analysis showing the diagnostic performance of suPAR for predicting significant fibrosis (F≥2).

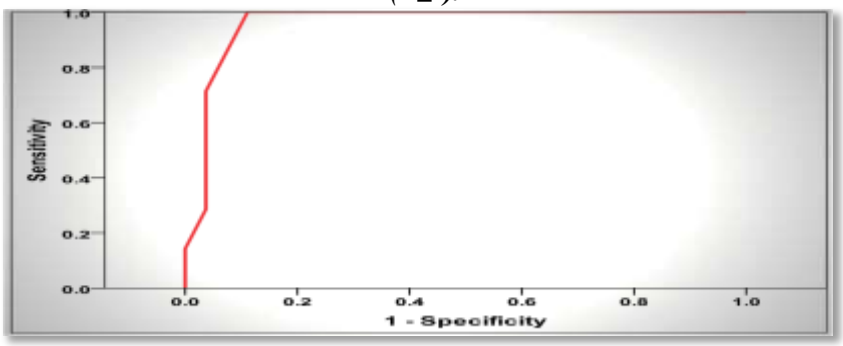

Figure (5): ROC curve analysis showing the diagnostic performance of suPAR for predicting advanced fibrosis (F≥3).

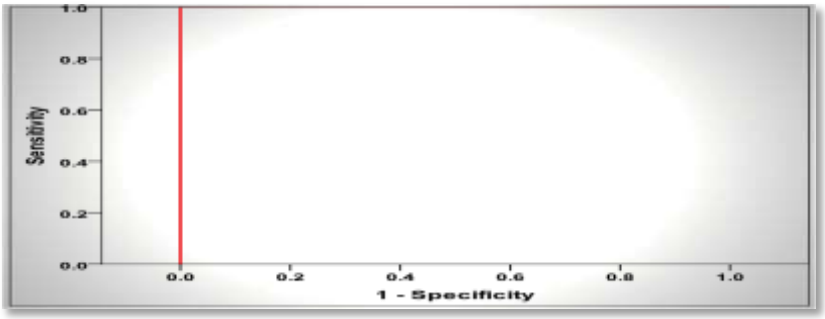

Figure (6): ROC curve analysis showing the diagnostic performance of suPAR for predicting cirrhosis (F4).

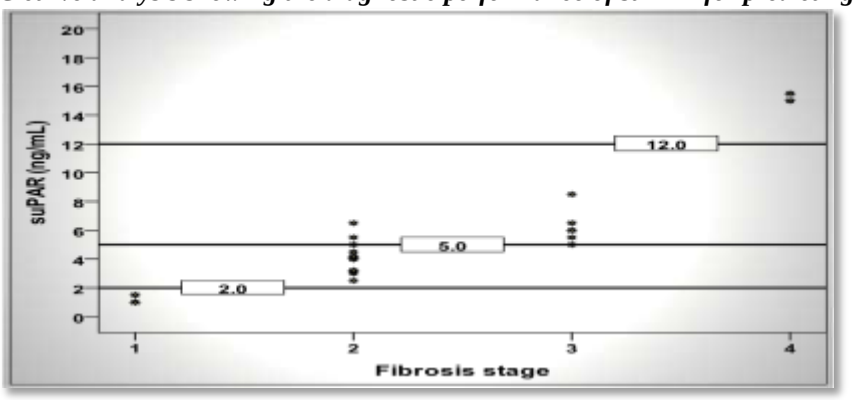

Figure (7): Diagnostic characteristics of suggested suPAR cutoff points in differentiating fibrosis stages.

Discussion

In patients with chronic hepatitis C, precise staging of liver fibrosis is important not only for estimation of prognosis, but also for indication of antiviral therapy. Liver biopsy is considered the reference method for evaluation of liver fibrosis in chronic hepatitis C patients(20).The risk benefit ratio of liver biopsy is insufficient to maintain it as a first line procedure, hence new and non-invasive criteria for evaluation of liver fibrosis are urgently needed(21).As the aim of the current study was to evaluate use of serum suPAR to identify severity of liver fibrosis and activity in patient with chronic hepatitis c viral infection.

Regarding suPAR serum level among different stages of liver fibrosis, we found that there was a significant rise in suPAR level among F4 (15.3±0.3 ng/ml) followed by F3 (6.2±1.1 ng/ml) then F2 (4.0±1.0 ng/ml) and least among F1 (1.1±0.2 ng/ml) with high statistical significant difference (t test value=378.87, P<0.001). This was in agreement with *Berres et al.*, who reported that soluble urokinase plasminogen activator receptor is associated with progressive liver fibrosis in hepatitis C Infection, as they assessed suPAR serum levels in 146 chronically HCV infected patients by enzyme-linked immunosorbent assay and correlated them with biopsy-proven histologic stage of liver fibrosis and noninvasive liver fibrosis markers (aspartate transaminase to platelets ratio index score, transient elastography).Their study revealed that suPAR serum levels were strongly associated with the histologic stage of liver fibrosis. Although mean suPAR levels in patients with F1 and F2 fibrosis were not different from healthy control subjects but they were significantly increased at higher stages of liver fibrosis (F3 and F4, P<0.0001)(22) these findings were consistent with our study.This can be explained by that the fact coagulation cascades in which the thrombotic state is determined by low-grade inflammation, increased fibrin deposition and inadequate fibrinolysis, respectively(12).

In the study done by *Zhou et al.*,plasma suPAR levels were significantly higher among patients with severe chronic hepatitis B, those with moderate, mild chronic disease and those with acute hepatitis B (P<0.05),moreover the plasma suPA and suPAR markedly increased in the acute stage and dramatically decreased in the remission stage,

but in all stages levels exceeded those in healthy subjects(23).This can be explained by that, the impairment of fibrinolysis is thought to be due to the competitive binding of pro-uPA by fibrinolytically inactive suPAR (24).In the present study suPAR level among moderate activity (A2) was (6.3±4.5 ng/ml) compared to mild activity (A1) (1.1±0.2 ng/ml).with high significant statistical difference (t=2.8, P<0.001).

In the current study, the correlation between suPAR and different parameters in different stages of fibrosis and grade of activity were non-significant, although there was a significant positive correlation with different stages of liver fibrosis(r=0.921, P<0.001).

In the study conducted by *Berres et al.*,systemic suPAR levels correlated with liver fibrosis and inflammation in patients with chronic liver diseases in the absence of systemic inflammation and overt bacterial infection. Furthermore, the highest circulating suPAR levels in acutely ill medical patients were detected in patients with impaired liver function and chronic liver disease(22).

Sjöwall et al, evaluated role of serum suPAR as a noninvasive test to detect liver fibrosis in 82 well-characterized patients with nonalcoholic fatty liver disease (NAFLD), suPAR levels were associated with severity of fibrosis in NAFLD, but did not correlate with inflammation(25).

There was a significant positive correlation between suPAR and αFP in different stages of liver fibrosis (r=0.383, P<0.018**)** this was consistent with *Mizejewski***,** who suggested that increased αFP-production in patients with liver cirrhosis might reflect, largely and abnormal or altered liver cell regeneration. High αFP serum levels have been found in 60–70% of patients with HCC(26).This may point to the role of suPAR in carcinogenesis as discussed previously by *Zhou et al. and Mekkawy et al.*,,who showed that uPA and uPAR, were elevated in hepatocellular carcinoma (HCC) in comparison to normal liver tissues(9,27).

Using multivariate linear regression analysis of different factors affecting suPAR, the stage of fibrosis was the only significantly independent factor associated with rise of suPAR. Regarding possible role of suPAR as a predictive factor for discriminating cirrhosis and severe liver affection in the present study using ROC analysis, we found that suPAR can be used to differentiate cirrhosis with cut-off value ≥12 ng/ml with sensitivity (100.%) and specificity of (100%), Area Under Curve (AUC)= (1), moreover, suPAR was found to predict advanced fibrosis F≥ 3 ng/ml with cut-off value **≥ 5** ng/ml with sensitivity (100.%) and specificity (85.2%), AUC (0.973), significant fibrosis F≥ 2 was ≥2.0 ng/ml with sensitivity of (100%) and specificity of (100.%), AUC=(1) this was consistent with *Haupt et al.,* who reported that elevated levels of suPAR has prognostic significance in end-stage cirrhotic patients(28*). Berres et al.*,found that suPAR values had a high diagnostic specificity and sensitivity to differentiate mild/moderate fibrosis (F1/F2) from severe fibrosis (F3/F4) with an area under curve of 0.774 (P=0.0001) and for the differentiation of non cirrhosis from cirrhosis (F1/F2/F3 vs. F4, area under curve 0.791, P=0.0001)(22).

Zimmermann et al., reported that Soluble urokinase plasminogen activator receptor is compartmentally regulated in decompensated cirrhosis and indicates immune activation and short-term mortality and found that serum and ascitic suPAR levels provided distinct, but relevant prognostic information on the severity of complications in patients with end-stage liver disease(29).

On the other hand the ROC analysis for prediction of grade of activity, the cut-off value ≥3.0 ng/mL can discriminate between moderate activity and mild activity with sensitivity of (94.1%) and specificity of (100%), AUC=(0.980).

So we suggest that serum suPAR level could be used as a non-invasive biomarker in predicting severity of hepatic fibrosis and grade of activity in chronic hepatitis C virus infection, in order to restrict the use of liver biopsy complementary to plasma suPAR level to those patients with significant fibrosis (F≥2) with cut off value of serum uPAR ≥2.0ng/ml with exclusion of those with F=4 cirrhotic patients with cut-off value of ≥12ng/ml.

Conclusion

Levels of suPAR were significantly correlated and increased with advanced stages of liver fibrosis and grades of activity. Stage of liver fibrosis was the only independent factor associated with rise in suPAR level. So, serum suPAR can be used as a good non invasive biomarker in predicting severity of liver fibrosis and activity in patients with chronic hepatitis C viral infection.

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