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E-mail: submit@mutagens.co.in
researchsubmission@hotmail.com

Research Paper

SERUM IL-27 AND RISK FOR HEPATOCELLULAR CARCINOMA IN EGYPTIAN HCV PATIENTS

Maha Houssen[1], Mona Abo bakr El-Hussiny[2], Neven Farouk Abbas[3], Ola Ali Elemam[2] and Enas Elkhamisy[3]

1- *Biochemistry department, Faculty of pharmacy , Damanhour University Egypt*
2-Clinical pathology department, faculty of medicine, mansoura university Egypt
3-Internal medicine department, faculty of medicine, Mansoura University, Egypt.

Abstract

The hepatitis B and C viruses are considered major factors associated with the development of HCC, due to their role in induction of chronic inflammation which is mediated by various cytokines**.** Inflammatory cytokines were considered to play a determinant role in the development and progression of both hepatitis C virus (HCV) and hepatocellular carcinoma (HCC). Interleukin 27 (IL-27) is helical cytokine belonging to the IL-6/IL-12 cytokine family with a broad range of dual proinflammatory /anti-inflammatory effects. To assess the serum levels of (IL-27) as proinflammatory/ anti-inflammatory cytokine in early detected HCV and HCV associated with HCC patients and to assess the correlations between its levels and liver enzymes activities , viral load as assessed by Polymerase chain reaction (PCR), Alpha fetoprotein level (AFP) and tumor stage. A total of Sixty one HCV and HCV with associated HCC patients, along with 20 healthy controls, were enrolled in the study. Serum levels of IL-27 were assessed using enzyme linked immunosorbent assay (ELISA). Serum viral load was assessed by PCR, AFP and liver enzymes were also assessed. The sensitivity of AFP and IL-27 as assessed by area under curve using ROC analysis were (AUC = 0.837) & (AUC = 0.768) respectively. Mean serum levels of IL-27 in patients with HCC 14.5± 4.8 ng/L were significantly elevated as compared to either HCV patients (6.4 ± 2.8 ng/L) or healthy control group (1.1 ±0.7 ng/L). Serum IL-27 was positively correlated with serum AST activity and serum viral load as assessed by quantitative PCR titer. This study showed that serum IL-27 may be a suspected novel marker for HCC in HCV patients.

Key words: HCV, HCC, IL-27, AFP.

INTRODUCTION

Hepatocellular carcinoma (HCC) is a worldwide malignancy with a high rate of metastasis **[1,2]**.The hepatitis B and C viruses are considered major factors associated with the development of HCC, due to their role in induction of chronic inflammation which is mediated by various cytokines **[3,4].** In Egypt, HCC was reported to account for about 4.7% of chronic liver disease patients with a doubling in the incidence rate in the past 10 years **[5, 6].**

The evolution of cell and immune markers such as cytokines is important to understand viral induced liver cancers in humans. The circulating immune based HCC biomarkers are vital candidates to successfully develop strategies to restrain liver injury **[4]**. IL-27 is a

hetrerodimeric type 1 cytokine that consists of two subunits IL-27 p28 and Epstein–Barr virus (EBV)-induced gene 3 (EB13) **[7, 8] .**It is a member of the IL-6 family of cytokines, which includes IL-12 and IL-23; like IL-12, it is secreted by activated antigen presenting cells and was originally reported to induce the formation of antiviral Th1 cells. IL-27 acts on naive CD4+ T cells and acts as a proinflammatory cytokine via initiation of type 1 helper differentiation and also has an anti-inflammatory activity through the induction of proinflammatory cytokine expression such as IL-10 **[9].** Besides its role in immune response, recent studies suggest that IL-27 may inhibit HCV replication in hepatocytes. Moreover, antitumor activity was also assigned to IL-27 **[10, 11].** On this basis, the aim of the present study was to assess the serum levels of IL-27 in group of HCV patients and HCV patients associated with HCC, to investigate the correlation between its levels with clinical pathological parameters such as viral load, liver enzymes activity and cancer stage among studied patients and to compare its sensitivity as a suspected HCC marker with alpha fetoprotein (AFP) as the standard HCC marker.

Subjects and methods:

Subjects

The present study is an observational case control study, conducted on two groups of patients along with sex and aged matched 20 healthy control volunteers.

Group 1 included 20 healthy control volunteers

Group 2 included 31 early **detected treatments naive,** unselected HCV patients attending the outpatient clinics of the internal medicine and the Hepatology unit, Mansoura university, during the period December 2014 to April2015. The diagnosis of HCV was confirmed by HCV m RNA quantitative PCR test.

Group 3 included 30 **early detected treatment naive HCC** patients attending the outpatient clinics of the Oncology Center-Mansoura University, during the period December 2012 to January 2015. The size and number of HCCs were defined by triphasic computerized scan or magnetic resonance imaging of the abdomen. The patients were staged and managed according to the Barcelona-Clinic Liver Cancer Group diagnostic and treatment strategy (BCLC) **[17].**

All subjects were genetically unrelated**.** Exclusion criteria were: patients with HBV, history of interferon therapy, history of drug hepatotoxicity, autoimmune liver disease, metabolic liver diseases and any other associated cancer.

The study was approved by the ethical committee of Mansoura University , faculty of Medicine, every study participant gave informed consent.

Sample collection:

Seven ml venous blood samples were withdrawn from each patient and divided as follow; 1.8ml into prothrombin tube for INR, 1ml into EDTA tube for CBC, and the rest into plain tube, left to clot and serum were separated into two aliquots, one used for liver function and the other was stored at -20°C for AFP and IL27 assay.

Biochemical analyses:

CBC was analyzed using automated counter, Sysmex KX-21, USA. Routine laboratory tests (albumin, total bilirubin, ALT, AST) were analyzed using (Dimension RXL MAX DADE BEHRING. Inc., Newark, DE, 19714-6101-USA).Serum AFP was assayed by ELISA using (R & D systems Inc., USA**) [18].** HCV mRNA was detected by quantitative polymerase chain reaction (PCR) using (Robogene HCV quantitation kits, Germany) **[19].** Serum IL-27 levels were detected by enzyme-linked immunosorbent assay (ELISA) technique using Glory science CO with detection range (1.6 ng/l-75 ng/l) **[20]**.

Statistical analysis:

All statistical analyses were performed using SPSS for windows version 20.0 (SPSS, Chicago, IL). Continuous data were expressed as mean ±standard deviation (SD), while categorical data were expressed in number and percentage. The differences among the groups were determined using one way analysis of variance (ANOVA test) for continuous data or chi-square test for categorical data. Correlations between variables were assessed using the correlation co-efficient test. Receiver operating characteristic (ROC) curves were generated to assess the diagnostic

accuracy of AFP and IL-27 in the differentiation between patients with HCC from those with HCV, and the area under the ROC curve (AUC) were used to assess the sensitivity and specificity of these markers. Statistical significance was set at $p<0.05$.

RESULTS:

All enrolled participants were divided into three groups. There were 31 HCV patients , 30 HCC patients along with 20 sex and aged matched healthy control. The clinical characters of all studied patients are presented in **(Table 1).**

One –way ANOVA with the three groups of participants and with the serum ALT & AST as the dependent variables showed that there were significant differences between groups in serum ALT **(F= 8.871,P<0.001)** and AST activities ***(F=*13.579*, P<0.001).*** As regard to the serum bilirubin and albumin there were significant differences between groups in serum bilirubin ***(F=11.968, P<0.001)*** and albumin ***(F=136.346, P<0.001).*** One –way ANOVA with the three groups of participants and with the serum INR, hemoglobin and platelets count as the dependent variables showed that there were significant differences between groups in serum INR ***(F=31.100, P<0.001),*** hemoglobin ***F= 50.842, P<0.001*****) and** platelets count (***F=38.583 , P<0.001***). One –way ANOVA with the three groups of participants and with the Serum AFP and IL-27 as dependent variables showed that there were significant differences in AFP ***(F=24.076, P<0.001)*** and IL-27 ***(F=99.967, P<0.001)*** **(Table 2).**

A non significant association was detected between serum IL-27 and cancer stage among HCC patients (P=0.181) **(Fig1).** The correlation analysis within HCC patients revealed significant correlation between serum IL-27 and serum AST activity **(r=0.485, p 0.0007)**. **Fig 3**

The correlation analysis within HCV patients revealed negative significant correlation between serum IL-27 and serum viral load as assessed by HCV PCR ***(r= 0.827, P<0.001)*** **Table 3.**

The ROC analysis to assess the sensitivity of both AFP and IL-27 as it was revealed that the ability of AFP & IL-27 in the discrimination between the HCV and HCC patients as measured by the area under curve (AUC) were **(0.837 & 0.768)** respectively**.** By using a cut off value > 12 ng/ml, IL27 had a sensitivity of 63.33% and Specificity of 100%. As regard AFP, at a cut off value > 20 ng/ml, the sensitivity was 80% and the specificity was 67.74 % **(Figure 4 &Figure 5).**

DISCUSSION:

The role of (HCV) infection as a risk factor for HCC is a subject of intense research **[21].** To elucidate the possible malignant transition to HCC among HCV patients, we studied the association of IL-27 with susceptibility to HCC in a group of HCV patients. To the best of our knowledge this is the first study to examine the association of serum IL-27 as host risk factor for HCC in a group of Egyptian HCV patients. In this study the first main observation is that HCV &HCC patients showed increased levels of serum IL-27 which is most elevated in HCC patients. This was in agreement with the study of **Zhu *et al* [22]** who demonstrated that IL-27 gene expression was enhanced in patients with liver cirrhosis or hepatocellular carcinoma. This coincides well with the systemic inflammatory role of IL-27 as it promotes naïve CD4+ T cell proliferation and IFN-γ production. This effect is dependent on STAT1-mediated T-bet activation, which induces IL-12Rβ2 expression thereby sensitize T cells to Th1 prone signals **[23, 24].** The elevated serum IL-27 levels in HCV patients compared to control may also be related to the antiviral activity of IL-27 as it was reported that IL-27 is able to induce many antiviral STAT1-dependent genes, and has an action similar to that of IFN alpha in protecting hepatocytes from viral infection **[25].** Although IL-27 has been shown to induce IL-10 expression which is linked to both elevated viral titers and an increase in the incidence of hepatocellular carcinoma through activation of STAT3 it inhibits expression of forkhead box P3, the critical transcription factor for T regulatory cells that have been implicated in sustaining viral persistence **[26, 27].** Moreover **Bender et al. [28]** show that IL-27 activates STAT3 in hepatocytes, but to a degree insufficient to activate any STAT3 candidate genes. They also noticed that IL-27 is a weak inducer of STAT3 phosphorylation in hepatocytes and a potent inducer of STAT1; it shares this property with the antiviral IFNs.

The negative correlation exists between serum IL-27 and viral load as detected by quantitative PCR titers assures the antiviral activity of IL-27 which is mediated by IFN-inducible antiviral genes such as myoxvirus protein 1, 2'-5'-oligoadenylate synthetase 2 and RNA- dependent protein kinase in macrophages, **[29]**. The correlation analysis also revealed positive correlation between IL-27 and AST activity in HCC patients; this is attributed to the role of IL-27 on hepatic stellate cells as it regulates STAT1-dependent genes which is a negative regulator of liver fibrosis **[30,31].** Regarding HCC patients, the elevated levels of serum IL-27 is ascribed to its role in hampering cancer progression as it was documented that IL-27 promotes anti-tumor CTL responses through directly stimulating CD8+ T cells **[32].** In addition, IL-27 can enhance anti-tumor CTL responses via enhancing CTL survival without reducing cytolytic activity. Moreover, IL-27 is also likely to influence CTL responses via affecting Treg, and Th17 (producing IL-10 and IL-21) and myeloid cells **[33, 34]**.

Comparing the sensitivity of IL-27 in discriminating between HCV and HCC with the AFP using ROC analysis we found that at cut off value > 12 ng/ml, IL27 had a sensitivity of 63.33% and Specificity of 100%. As regard AFP, at a cut off value > 20 ng/ml, the sensitivity was 80% and the specificity was 67.74 %. ***(*Cabrena *et al.,[*35]** found that α-fetoprotein (AFP) had a sensitivity of 53.8% and a specificity of 86.8% at a cut-off value of 32.8 ng/ml (AUC=0.755; P<0.0001). The area under curve in case of AFP is (AUC = 0.837) and IL-27 is (**AUC = 0.768)**. This was in agreement with the Fan ***et al*** **[36]** who found that the area under the curve (AUC) of IL-27 and AFP were (0.804) and (0.818), respectively. Thus, IL-27 may be a novel suspected marker for HCC and a candidate for HCC immunotherapy. Further research studies are warranted to investigate the effect of IL-27 systemic administration and to assess susceptible side effects.

Table 1. Clinical characteristics of patients

Parameters	Control (n=20)	HCV (n=31)	HCC (n=30)	ANOVA test F p
Age (years) Mean ±SD	48.8±6	49. ±7.4	52.8 ±6.7	2.581 0.082
Sex (n)				
Female	(9) 45%	(15) 48,4%	(12) 40%	0.438 0.803
Male	(11) 55%	(16) 51.6%	(18) 60%	
Clinical presentation				
Asymptomatic		(20) 64.5%	(0) 0%	28.796 <0.001
Jaundice		(2) 6.5%	0, 0%	2.001 0.157
Fatigue		(9) 29%	0, 0%	10.217 0.0013
Pre-coma		(0) 0%	7, 23.3%	8.171 0.004
Weight loss		(0) 0%	5, 16.7%	5.628 0.018
Abdominal pain		(0) 0%	9, 29%	10.91 <0.001
Bleeding		(0) 0%	9, 29%	10.91 <0.001

HCV: Hepatitis C Virus **HCC:** Hepatocellular carcinoma

Table 2: Biochemical parameters of the studied groups:

Biochemical parameter	**Control (n=20)**	**HCV (n=31)**	**HCC (n=30)**	**ANOVA test**	
				F	**p-value**
ALT (U/L): Mean ±SD	20.8 ±5.9	45.4 ±20.3	47.7 ±32.9	8.871	**<0.001**
AST (U/L): Mean ±SD	21.9 ±5.9	48.9 ±36.4	71.9 ±40	13.579	**<0.001**
Bilirubin (mg/dl): Mean ±SD	0.6 ±0.2	0.9 ±0.5	3.7 ±4.2	11.968	**<0.001**
Albumin (gm/dl) Mean ±SD	4.5 ±0.5	3.9 ±0.5	2.2 ±0.6	136.346	**<0.001**
INR Mean ±SD	1 ±0.03	1.1 ±0.2	1.6 ±0.5	31.100	**<0.001**
Hb (gm/dl) Mean ±SD	14.5 ±1.1	12.7 ±1.9	9.9 ±1.6	50.842	**<0.001**
WBCs (x10^3 /cmm) Mean ±SD	5.4 ±1.5	6.7 ±2.7	7.5 ±2.9	4.346	0.016
PLT (x10^3 /cmm) Mean ±SD	232.7±45.6	174. ±50.2	111.9 ±42	38.583	**<0.001**
Viral load (PCR) (x10^5)IU/ml **Mean ±SD**	----------	6.9 ±4.8	----------		
AFP (ng/ml) Mean ±SD	4.3 ±1.5	14.7 ±7.8	117±109.3	24.076	**<0.001**
IL-27 **(ng/l) Mean ±SD**	1.1 ±0.7	6.4 ±2.8	14.5 ±4.8	99.967	**<0.001**

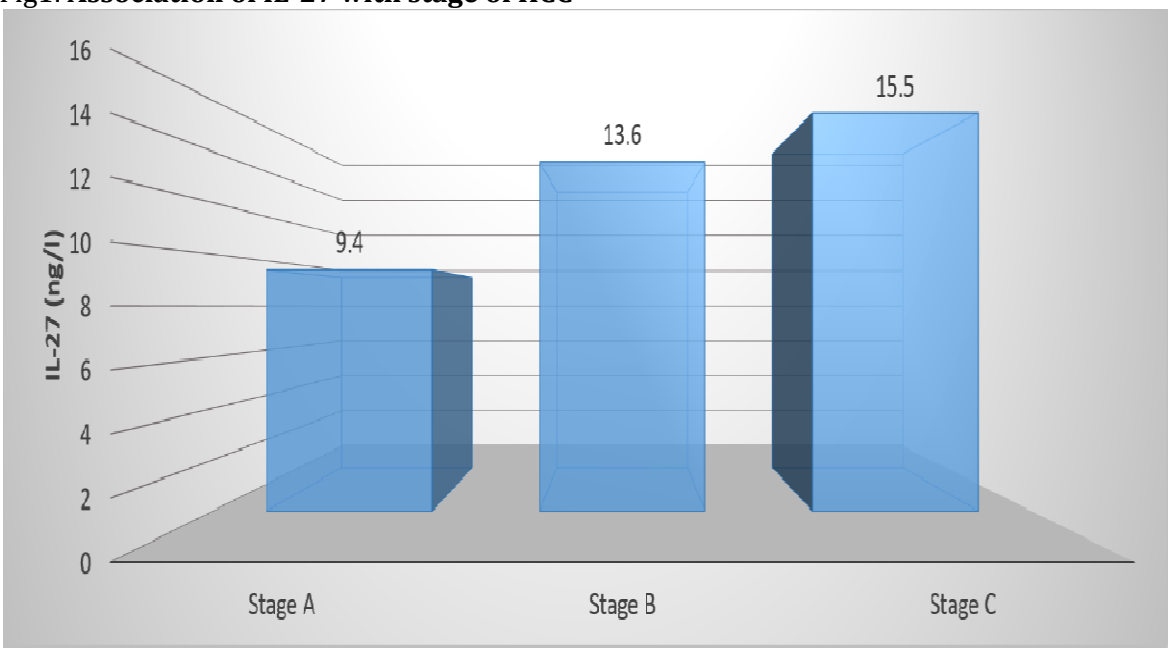
AST: Aspartate aminotransferase **ALT: Alanine aminotransferase**
INR: International normalized ratio **Hb: Hemoglobin**
WBCS: White blood cell **PLT: Plateletes**
AFP: Alphaphetoprotein **PCR: Polymerase chain reaction**
IL-27: Interleukin 27
HCV: Hepatitis c Virus **HCC: Hepatocellular carcinoma**

Table 3: Correlations of IL27 with ALT, AST and PCR

	HCV group		HCC group	
	r	p	r	p
IL-27 with ALT	-0.343	0.059	0.272	0.146
IL-27 with AST	-0.080	0.669	0.485	0.007
IL-27 with PCR	-0.827	<0.001		

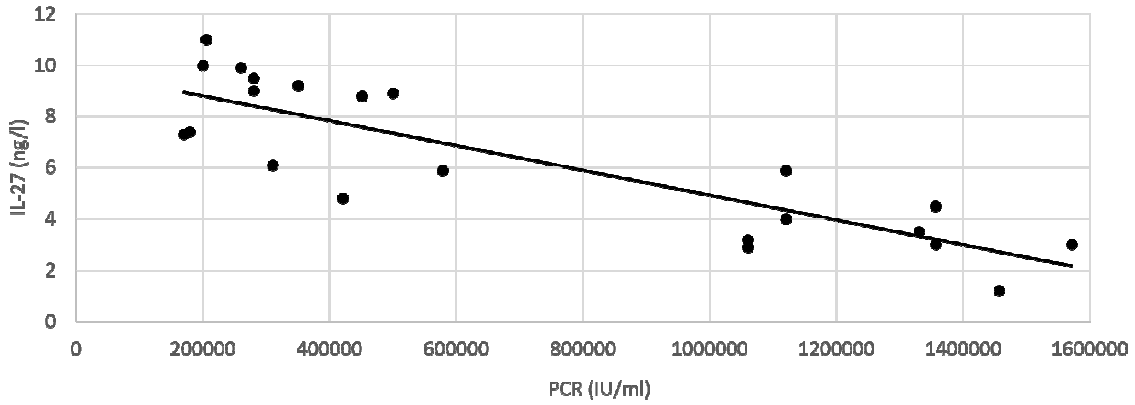
IL-27: Interleukin 27
AST: Aspartate aminotransferase
ALT: Alanine aminotransferase
PCR: Polymerase chain reaction
HCV: Hepatitis C virus
HCC: Hepatocellular carcinoma

Fig1: **Association of IL-27 with stage of HCC**



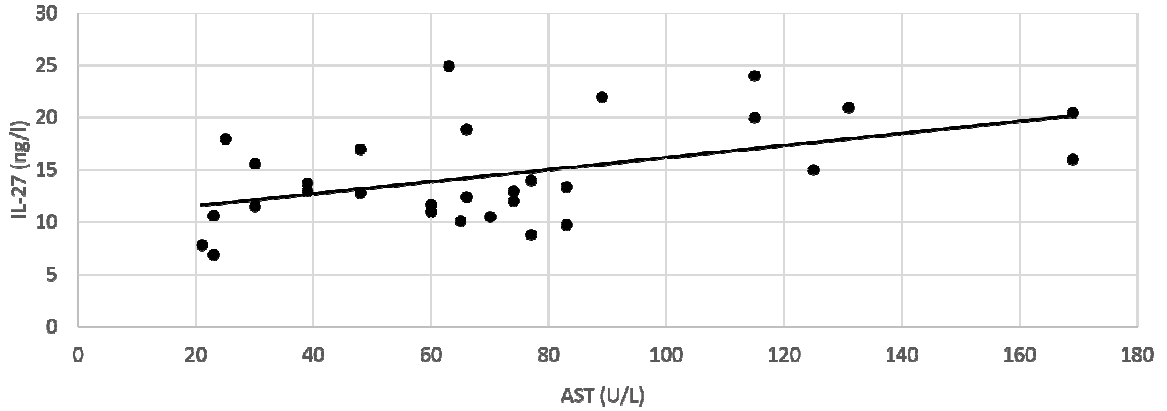
IL-27: Interleukin 27 **HCC**: Hepatocellular carcinoma

Fig 2: Correlation between the viral load as assessed by PCR and the IL-27 in the HCV group (r= -0.827, p <0.001



PCR: Polymerase chain reaction **IL-27: Interleukin 27**

Fig 3: Correlation between the AST activity and the IL-27 in the HCC group (r=0.485 ,p 0.0007)



Il-27: interleukin 27 AST: Aspartate aminotransferase

Figure 4 : Roc curve represent the ability of the IL-27 in the discrimination between the HCV and HCC patients (AUC = 0.768)

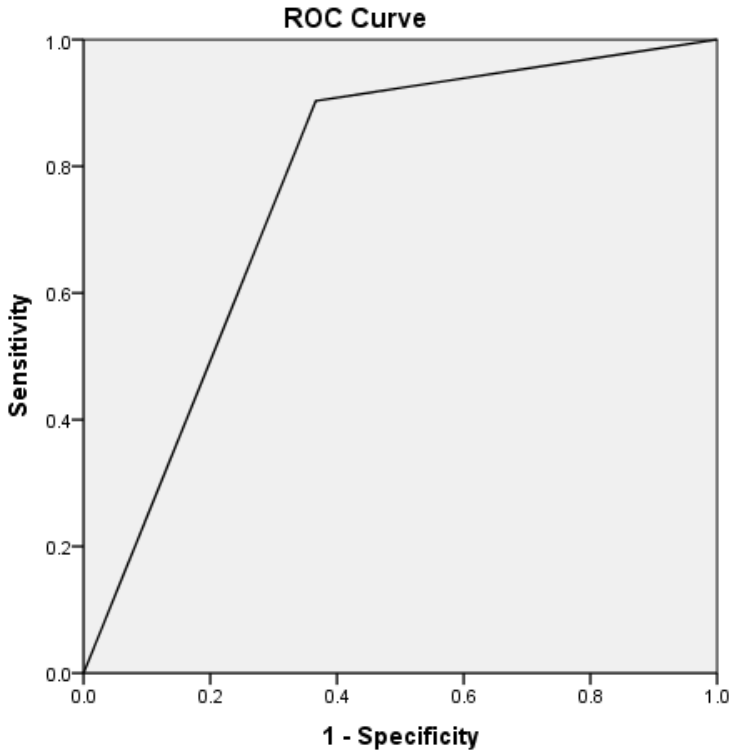
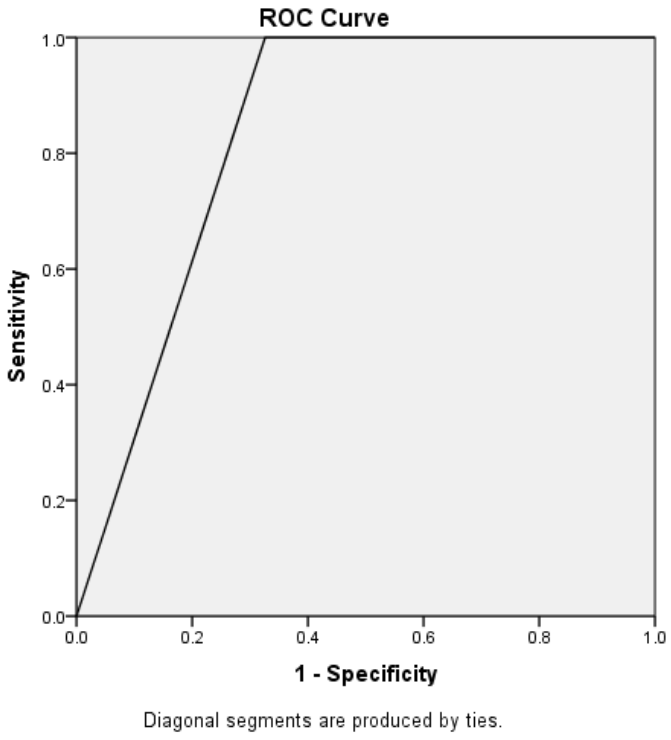


Figure 5: Roc curve represent the ability of the AFP in the discrimination between the HCV and HCC patients (AUC = 0.837)



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