Serum Interleukin 6 in Egyptian Cirrhotic Patients with Chronic hepatitis C related Hepatocellular carcinoma

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Abstract

Background: Hepatocellular carcinoma (HCC) is a worldwide health problem. **The aim** was to evaluate diagnostic and prognostic role of serum Interleukin 6 (IL6) in Egyptian patients with chronic hepatitis C related HCC. **Methods**: This study was conducted on 80 Egyptian participants; 35 patients diagnosed as LC (group 1), 35 patients diagnosed as HCC (group 2), and10 apparently healthy individuals (group 3). All patients included in the study, were subjected to full history taking, thorough clinical examination, routine laboratory and radiological investigations. Additionally, quantitative measurement of serum IL-6 and AFP levels using an ELISA were done for all patients and controls. **Results:** HCC was presented more in males (51.4%) than females (48.6%) with a mean age of 61.89 ±8.22 years. AFP and IL-6 levels were significantly higher in HCC group (group 2) than in liver cirrhosis group (group 1). IL6 at a cutoff point of (45.65pg/ml), showed a sensitivity of 85.7%, a specificity of 82.9%, PPV of 83.3, NPV of 85.3 and AUC=0.858, Comparing AUCs, revealed that combined (AFP+IL6) was significantly better than each marker alone. Serum IL-6 level was higher in patients with Child class B than child class A patients. **Conclusion**: Serum level of IL-6 can represent a potential beneficial biomarker for diagnosis of hepatocellular carcinoma with good sensitivity especially if combined with AFP but with low specificity and may have a limited role in prognosis of hepatocellular carcinoma.

Keywords: Interleukin 6; hepatitis C; Hepatocellular carcinoma; Alpha –fetoprotein

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common malignancy worldwide and the second most common cause of cancer-related death) (1).

In Egypt, HCC is a serious if not the most serious cancer problem (2). In Egypt and over the decade, a remarkable growth of HCC (from 4.0 % to 7.2 %) was observed in the patients with chronic liver disease patients (3). HCC is the fourth most common cancer and the second cause of cancer related mortality in both sexes among the Egyptian populations (4).

The development of cirrhosis is associated with high risk for developing HCC with most common risk factors including alcohol, nonalcoholic fatty liver disease (NAFLD),obesity, diabetes, smoking, aflatoxin, viral hepatitis as hepatitis B virus (HBV), and hepatitis C virus (HCV) (3).

Guidelines for diagnosis of HCC according to the American Association for the Study of Liver Disease (AASLD) is based on imaging characteristics (arterial phase enhancement and venous or delayed phase washout) by one of imaging technique (Triphasic spiral CT or MRI) (4).

Interleukin 6 (IL6) is a pleiotropic cytokine. IL6 regulates the response of certain liver specific transcription factors. In addition, IL6 plays a central role in hematopoiesis, as well as in the differentiation and growth of a number of cells of different histologic origin, as: endothelial cells, keratinocytes, neural cells, osteoclasts, and osteoblasts. IL 6 regulates cell growth and act as a paracrine and autocrine growth factor in different malignancies. Levels of IL 6 play a role of in proliferation of cancer cells in solid tumors (5).

IL 6 binds directly to hepatocyte by interacting with an 80 DK membrane glycoprotein (gp80) that complexes with a signal- transducing Tran's membrane molecule named gp130. Binding of gp130 leads to dimerization of the intracellular domains of two gp 130 molecules, which promotes association with receptor associated Janus kinases (JAKs: JAK1 - JAK2), tyrosine kinase and phosphorylation of different tyrosine residues on the gp130 molecule. Depending on the location of the phosphorylated tyrosine, signal transducer and cytoplasmic transcription proteins (STAT) mainly STAT3 become activated. STAT3 activation in the liver, which is associated with reduced apoptosis and accelerated proliferation of hepatocytes,

leading to enhanced HCC development (6). So, this study will focus on the role of IL 6 in HCC development, to assess its diagnostic and prognostic role.

The present study aimed to evaluate diagnostic and prognostic role of serum Interleukin 6 (IL6) in Egyptian patients with chronic hepatitis C related Hepatocellular carcinoma (HCC).

Patients and methods

This cross-sectional study included 70 patients, selected from those admitting in (Benha University Hospitals) and (Hospital of Shebin El-Kohom for Fevers, Hepatology and Gastro- entrology), in addition to (10) apparently healthy individuals of matched age and sex served as a control group during the period from August 2019 to April 2020) after approval of Benha university ethical committee of research .

Subjects were divided into 3 groups: **Group (1):** 35 patients with chronic hepatitis C related liver cirrhosis diagnosed by clinical, biochemical data and ultra- sonographic finding. **Group (2):** 35 patients with chronic hepatitis C related hepatocellular carcinoma diagnosed according to guidelines for diagnosis of HCC by: Magnetic resonance imaging (MRI) or Tri phasic spiral computed tomography (CT) criteria (arterial phase enhancement and venous or delayed phase washout). **Group (3):**10 apparently healthy subjects (age and sex matched) served as a control group.

Informed consent was obtained from all participants. The study will be approved by the local ethics committee of research involving human subjects of Benha faculty of medicine.

Inclusion criteria:

- Age > 18 years
- Both sexes were included
- Chronic hepatitis C

Exclusion criteria:

- Age less than 18 years.
- Extra hepatic malignancies.
- Non Hepatitis C Virus (HCV) related liver cirrhosis diseases:

Patients with chronic HBV infection, auto-immune hepatitis, metabolic liver disease, non-alcoholic steato-hepatitis and alcoholic hepatitis.

All patients were subjected to full medical history, thorough clinical examination, laboratory investigations as CBC and ESR, liver profile: (Serum albumin, serum bilirubin level, serum AST, serum ALT, INR), Random blood sugar, Kidney function tests (Blood urea, serum creatinine), Serum Alfa- fetoprotein (AFP), Serum Interleukin 6 (IL6) and radiological investigation: pelvis-

abdominal ultrasound , tri-phasic spiral computed tomography (CT) for abdomen to assess criteria for HCC diagnosis (arterial phase enhancement and venous or delayed phase washout) .

Assessment of prognosis in patients with HCC through evaluation of its correlation with variable prognostic factors:

(I) Child -Pugh score: This score depends on 5 variables (serum bilirubin, serum albumin, ascites, hepatic encephalopathy, prothrombin time (7)**.**

(II)Model for End Liver Disease (MELD)

It depends on serum bilirubin, serum creatinine and the international normalized ratio for prothrombin time (INR). It is calculated according to the following formula:

MELD= 9.57 x log [serum creatinine (mg/dl)] + 3.78 x log [serum bilirubin (mg/dl)] + 11.2 x log [INR] +6.43. (IV) Portal vein thrombosis (8)

(III) **Barcelona - Clinic Liver Cancer (BCLC) staging system:** It depends on tumor size, performance status (PS) and the Child -Pugh score (9).

Serum Interleukin 6; The kit uses a double-antibody sandwich enzyme-linked immune sorbent assay (ELISA) to assay the level of Human Interleukin 6(IL-6) in samples (Human IL6 Immunoassay, sunred biological technology) : Add Interleukin 6 (IL-6) to mono clonal antibody Enzyme well which is pre-coated with Human Interleukin 6 (IL-6) monoclonal antibody incubation; then add Interleukin 6 (IL-6) antibodies labeled with biotin, and combined with Streptavidin-HRP to form immune complex; then carry out incubation and washing again to remove the uncombined enzyme. Then add Chromogen Solution A, B, the color of the liquid changes into the blue, and at the effect of acid, the color finally becomes yellow. The chroma of color and the concentration of the Human Substance Interleukin 6(IL-6) of sample were positively correlated)

Statistical analysis:

Results were collected, tabulated, statistically analyzed by statistical package SPSS version 20. Two types of statistics were done; Descriptive: e.g. percentage (%), mean and standard deviation SD. Analytical: Student's t-test: It is a single test used to collectively indicate the presence of any significant difference between two groups for a normally distributed quantitative variable. Mann-Whitney test: it is a nonparametric test of Student's t-test. It is used to collectively indicate the presence of any significant difference between two groups for a not normally distributed quantitative variable. Chi-Squared ($\chi 2$): It is used to compare

between two groups or more regarding one qualitative variable in 2x2 contingency table or r c complex table. Fisher's exact test: It is used to compare between two groups regarding one qualitative variable in a 2x2 contingency table when the expected count of any of the cells less than 5. Wilcoxon signed rank test: It is the non-parametric version of Paired t test. It is a single test used to collectively indicate the presence of any significant difference between different time sequences for a not normally distributed quantitative variable. Correlation analysis: Spearman correlation was used to assess the strength of association between two quantitative variables. The correlation coefficient defines the strength and direction of the linear relationship between two variables. Receiver operating characteristic (ROC curve): is a graphical plot of the sensitivity, vs. false positive rate (one minus the specificity). The ROC is also known as a Relative Operating Characteristic curve, because it is a comparison of two operating characteristics (TPR & FPR).

Results

The present study was conducted on 35 cases of LC (group1), their mean age was (59.14±11.48) years. They included 18 males (51.4%) and 17 females (48.6%). In addition to 35 cases of HCC (group 2). Their mean age was (61.89 ±8.22) years. They were 18 males (51.4%) and 17 females (48.6%). A third group of 10 apparently healthy subjects, their mean age was (64.2±8.93) years. They included 5 males (50%) and 5 females (50%). They were of matched age and gender for HCC and LC groups. No statistically significant differences were found as regarding (gender, occupation, marital status, smoking and alcohol consumption) among studied cases as shown in figure (1,2) .

GIT bleeding was presented more common in LC group than HCC group with significant difference. No statistically significant differences were found regarding the (jaundice, hepatic encephalopathy and abdominal pain) between HCC and LC groups as shown in table (1).

Fever and lower limb edema were more present in LC group with significant difference when compared to HCC group and no significant difference was detected as regarding (pallor, flapping tremors and palmer erythema) between HCC and LC as shown in table (1).

No statistically significant differences were found regarding (DM and HTN) between HCC and LC groups as shown in table (1). .

Hepatomegaly, splenomegaly and ascites according to ultra-son graphic finding were more present with statistically significant in

LC group when compared to HCC group and no significant difference was found between HCC and LC groups regarding portal vein thrombosis as shown in table (1).

According to the complete blood picture, the mean hemoglobin level was (10.32±1.42 gm./dl) in HCC patients compared to (10. 17±1.76gm/dl) in patients with LC with no significant difference. The mean platelet count was (102.734±53.8) (103/cmm) in HCC patients compared to (112.371±27.6) (10^2/cmm) in patients with LC with no significant difference. INR was higher in LC group when compared to HCC group with statistically significant difference while ALT was higher in HCC group when compared to LC group with statistically significant difference, Serum albumin was lower in LC group when compared to HCC group with highly statistically significant difference and no significant differences were found between HCC and LC groups regarding (ESR, T. bilirubin, D. bilirubin, AST and S. creatinine)**,** as shown in table 2

IL-6 level was significantly higher in HCC when compared to control group and LC group as shown in table (3). AFP level was significantly higher in HCC when compared to LC group as shown in table (3).

IL-6 level was higher in patients with Child class B concentration (59.5pg/ml) than Child class C patients (57.3pg/ml) and Child class A patients (41.5pg/ml) but not reach significant correlation table (4). Serum IL-6 level was significantly higher in patients with Barcelona score B (64.6 pg/ml) than Barcelona stage (A) (54.3pg/ml) with significant correlation table (5).

There was no correlation were found between IL-6 level and (age ,HB ,PLT ,WBCS ,ESR ,RBS, s. albumin , t . bilirubin , d. bilirubin ,ALT ,AST ,INR ,creatinine and AFP) in HCC ,LC and control groups. table (6)

The diagnostic performance of serum IL-6 in HCC and control groups At a cut off value of 25.15, IL-6 showed a sensitivity of 100%, a specificity of 90%, PPV of 97.2, NPV of 100 and AUC=0.931 as shown in figure (3), table (7).

At a cut off value of 25.15pg/ml for IL-6 and cut off value of 8.1ng/ml for AFP showed a sensitivity of 100%, a specificity of 37.1%, PPV of 61.4%, NPV of 100% and AUC=0.686 as shown in Figure (4), (table 8).

Table (1) Comparison between HCC and LC Groups according to patient's characteristics

	Group(1) LC (35)		**Group(2) HCC (35)**		Statistical test (FET)	P value
	No	%	No	%		
Jaundice	7	20.0	7	20.0	0.0	1.0
Hepatic encephalopathy	13	37.1	7	20.0	X2=2.52	0.011
Abdominal pain	25	71.4	23	65.7	X2= 0.27	0.61
GIT Bleeding	15	42.9	5	14.3	7.0	**0.008****
Fever	8	22.9	0	0.0	6.92	**0.005****
Pallor	25	71.4	23	65.7	X2= 0.27	0.61
Flapping tremors	13	37.1	7	20.0	X2=2.52	0.11
Palmer erythema	13	37.1	7	20.0	X2=2.52	0.11
LL oedema	30	85.7	10	28.6	X2=23.33	**>0.001****
DM	14	40.0	14	40.0	0.0	1.0
HTN	13	37.1	8	22.9	X2= 1.7	0.19
Hepatomegaly	25	71.4	17	48.6	X2=5.71	**0.05***
Splenomegaly	32	91.4	25	71.4	X2=0.86	**0.03***
Ascites	33	94.3	10	28.6	X2=31.9	**>0.001****
PVT	0	0.0	3	8.6	X2=1.39	0.24

*X2 = Chi square *FET=Fisher exact test*GIT=gastrointestinal bleeding*DM=diabetes mellitus *HTN=hypertension *PVT=portal vein thrombosis

Table (2) Comparison between HCC and LC Groups according to laboratory investigation:

	Group(1) LC (35)	**Group(2) HCC (35)**	Statistical test (FET)	P value
HB gm/dl mean ±SD	10.17±1.76	10.32±1.42	St t= 0.38	0.71
Platelets(n/L) mean ±SD	112371.4± 64630.21	102734.3± 53780.7	St t= 0.68	0.50
WBCs(n/L)mean ±SD	5719.04 ±2766.11	5612.3 ±2437.04	St t= 0.17	0.86
ESR (mm/hr)mean ±SD	15.51±11.31	15.66±9.61	St t= 0.06	0.96
RBS(mg/dL)mean ±SD	174.34±37.37	185.91±49.42	St t= 1.11	0.27
S. albumin (g/dL) mean ±SD	2.94±0.65	3.4±0.50	St t= 3.36	**0.001****
T bilirubin(mg/dL) mean ±SD	1.59±0.92	1.24±0.69	St t= 1.8	0.08
D bilirubin (mg/dL) mean ±SD	0.89±0.53	0.69±0.44	St t= 1.66	0.10
ALT(I/U) mean ±SD	35.73±12.31	46.93±26.55	St t= 2.26	**0.027***
AST(I/U) mean ±SD	47.49±27.65	56.38±27.85	St t= 1.34	0.18
INR mean ±SD	1.38±0.30	1.24±0.20	St t= 2.27	**0.027***
S. creatinine (mg/dL) mean ±SD	1.08±0.24	1.05±0.23	St t= 0.45	0.65

SD, standard deviation *X2 = Chi square *FET=Fisher exact test

Table (3): Comparison of Serum IL-6 and AFP concentration among studied groups :

	Group (1) LC N=35	**Group (2) HCC N=35**	**Group (3) control N=10**	***P1***	***P2***	***P3***	***P4***
IL-6 mean ±SD (pg/ml)	35.97±39.28	96.05±96.4a	25.51±14.51b	**0.001**** St 8.06t	0.42 St t= 0.82	**0.027*** St t= 2.29	**0.001**** St t= 3.42
AFP mean ±SD (ng/ml)	9.86±9.78	342.84±802.17a	5.0±2.58	**0.025*** St t=3.87	0.13 St t=1.54	0.19 St t= 1.32	**0.017*** St t= 2.46

SD, standard deviation p1, comparison between control, LC and HCC; p2, comparison of LC versus control; p3, comparison of HCC versus control; p4, comparison between LC and HCC

Table (4): Correlation between IL-6 level and Child classes in HCC group:

Child score		**Median IL-6(pg/ml)**	IQR	Statistical test	P value
A	4	41.5	27.75-58.93	KW= 4.16	0.13
B	29	59.5	52.8-122.1		
C	2	57.3	50.5-		

*Kw:Kruskal Wallis test * IQR: Inter Quartile Range

Table (5): correlation between IL-6 level and Barcelona staging system in HCC group:

Barcelona staging system	N	**Median IL-6(pg/ml)**	IQR	Statistical test	P value
A	20	54.3	42.35-61.83	MW= 2.47	**0.014***
B	15	64.6	56.8-127.3		

IQR: Inter Quartile Range *N: number * M W:Mann Whitney test

Table (6): Correlation between IL-6 and other variables in each studied group:

	IL-6	LC group	HCC group	Control group
Age	Pearson Correlation	-.216-	.002	.412
	Sig. (2-tailed)	.213	.992	.237
HB	Pearson Correlation	-.106-	.265	-.305-
	Sig. (2-tailed)	.544	.124	.391
PLT	Pearson Correlation	-.027-	-.282-	.180
	Sig. (2-tailed)	.877	.101	.619
WBCS	Pearson Correlation	.078	-.043-	.818**
	Sig. (2-tailed)	.657	.807	.004
ESR	Pearson Correlation	-.114-	-.066-	.898**
	Sig. (2-tailed)	.514	.708	.000
RBS	Pearson Correlation	.262	-.186-	-.438-
	Sig. (2-tailed)	.129	.284	.206
S.albumin	Pearson Correlation	.025	-.181-	-.330-
	Sig. (2-tailed)	.888	.297	.352
T.Bil	Pearson Correlation	-.199-	.060	.301
	Sig. (2-tailed)	.251	.732	.399
D.Bil	Pearson Correlation	-.206-	-.063-	.405
	Sig. (2-tailed)	.236	.720	.246
ALT	Pearson Correlation	-.004-	.033	.506
	Sig. (2-tailed)	.981	.852	.136
AST	Pearson Correlation	-.090-	.042	.242
	Sig. (2-tailed)	.608	.812	.500
INR	Pearson Correlation	-.025-	.256	0
	Sig. (2-tailed)	.885	.138	0
Creatinine	Pearson Correlation	-.249-	.052	-.031-
	Sig. (2-tailed)	.148	.768	.931
AFP	Pearson Correlation	.098	-.190-	-.302-
	Sig. (2-tailed)	.576	.274	.396

Table (7): Diagnostic performance of serum IL-6 in HCC and control groups:

	IL-6(HCC& Control group)
AUC	0.931 (0.802-1.0)
Cutoff point	25.15
Sensitivity	100
Specificity	90.0
PPV	97.2
NPV	100
Accuracy	97.7

ROC, receiver operating characteristic curve; AUC, area under ROC curve; PPV, positive predictive value; NPV, negative predictive value

Table (8): Diagnostic performance of combined serum IL-6 and AFP in HCC and LC groups:

	Combined IL-6 +AFP (HCC&LC)
AUC	0.686 (0.559-0.812)
Cutoff point	8.1AFP + 25.15 IL-6
Sensitivity	100
Specificity	37.1
PPV	61.4
NPV	100
Accuracy	68.6

ROC, receiver operating characteristic curve; AUC, area under ROC curve; PPV, positive predictive value; NPV, negative predictive value

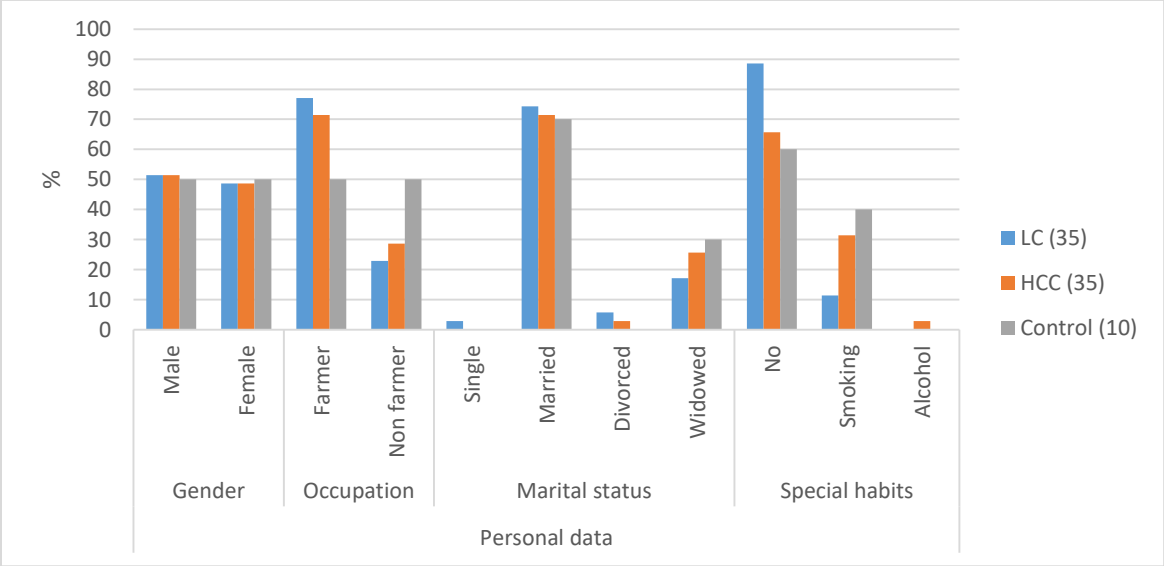

Figure (1) Personal History among studied cases.

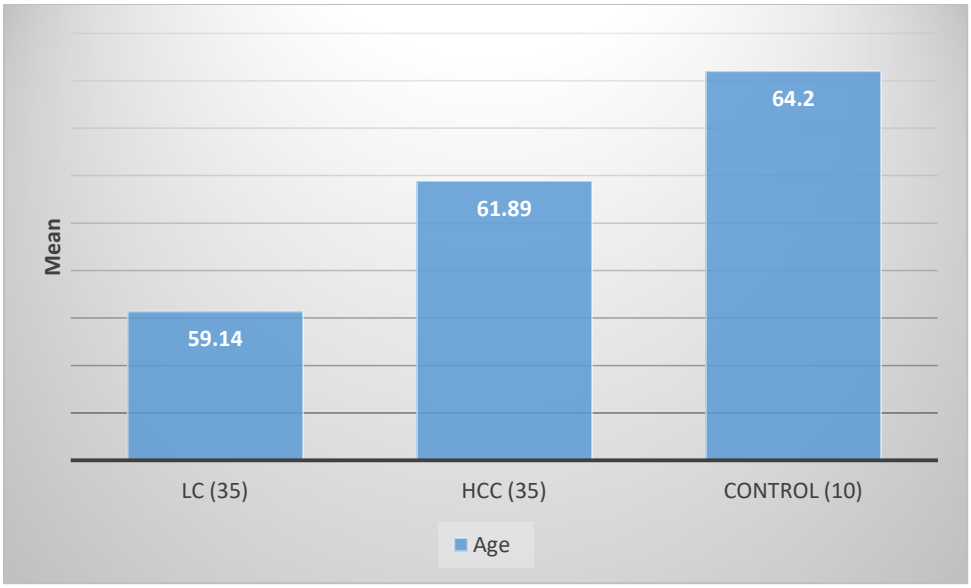

Figure (2) Age among studied cases.

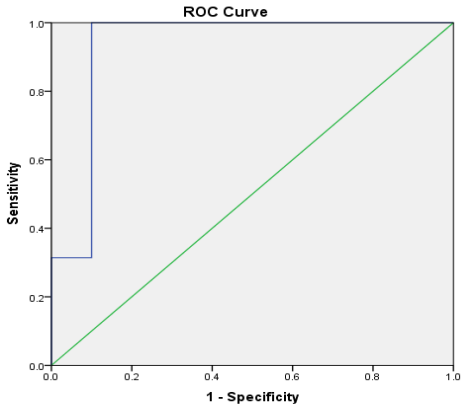

Figure (3): ROC curve of serum IL-6 for discrimination between HCC and control groups.

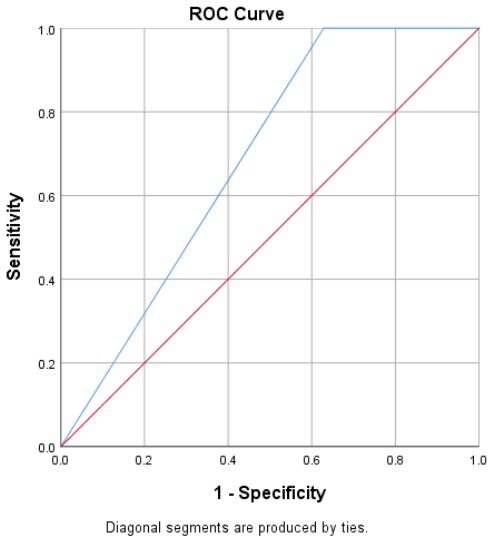

Figure (4): ROC curve of combined serum IL-6 and AFP for discrimination between HCC and LC groups.)

Discussion

Hepatocellular carcinoma (HCC) is a worldwide health problem. the commonest causes of HCC are chronic infections with hepatitis C and B, chronic liver inflammation caused by these viruses leading first to liver cirrhosis and, ultimately, to overt cancer (10),

Interleukin 6 (IL6) is a pleiotropic cytokine, during inflammation IL 6 play a role of in proliferation of cancer cells in solid tumors IL-6 was also shown to induce the expression of the mitogenic, motogenic, morphogenic and pro-neoangiogenic scatter factor hepatocyte growth factor which, besides being commonly expressed at high levels in HCC (11).

In the current study, HCC commonly higher presented in males (51.4%) than females (48.6%) with no significant difference, this comes in agreement with, El-Shahat and his colleagues (12) who reported a non-significant difference in sex distribution between HCC patients.

In the current study, IL-6 was highly significant in HCC when compared to LC and control group, in HCC group its mean was (96.05 ± 96.4a) and in LC group (35.97 ± 39.28), while in control group (25.51±14.51), IL-6 was highly significant in HCC group when compared to control group (P = 0.027), also there was high significant correlation between IL6 in HCC group when compared to LC group, but no significant correlation between LC and control group (P = 0.42) This was in agreement with Porta and his colleagues (13) reported that IL-6 titers were

4-fold higher in HCC vs. cirrhotic patients and 25-fold higher than in healthy controls, Also, a researcher and his colleagues (14) concluded that IL-6 levels in patients with liver cirrhosis associated HCC are higher than in patients with liver cirrhosis alone and controls, indicating that production of this cytokine is increased by tumor cells. AFP was significant in HCC (342.84 ± 802.17a) when compared to LC (9.86 ± 9.78).

Our results were not consistent also with another researcher and his colleagues (15) who found a significant decrease in serum IL-6 concentration in HCC patients as compared to patients with liver cirrhosis, their study included all etiology of liver cirrhosis and patients with other types of malignancy, advanced organ failure, active infection and advanced medical co-morbidity were excluded from the study.

In the current study, serum IL-6 level was higher in patients with Child class B (59.5pg/ml) followed by Child class C (57.3pg/ml))then A patients (41.5pg/ml) but not reach significant difference, an another and his colleagues (16) declared that no correlation was found between IL-6 level and the child scores in agreement to our results But this differs from that reported by a group of researchers (17) who declared that Compared to the patients with Child Pugh class A, the patients with Child Pugh class B had a significantly increased level of IL-6 with significant difference (P=0.002), this difference was due to their study did not exclude any cause for HCC.(18).

In the current study, serum IL-6 level was higher in patients with Barcelona score B (64.6pg/ml) than Barcelona score A patients (54.3pg/ml) with significant difference. In partial agreement to these results , a researcher and his colleagues (15) found that HCC patients showed increased serum IL-6 concentration with increased BCLC score, {IL6 level in Barcelona score A patients (75.59pg/ml) and Barcelona score B patients (82.18pg/ml) Barcelona score C patients (96.06pg/ml) with significant difference . In the current study, the results of the current study showed no correlation between IL-6 level and portal vein thrombosis; this comes in disagreement with a study done on 2018 (16) who declared that plasma IL-6 levels were found to be correlated with portal vein invasion.

In our study, correlations of IL6 level with studied data in HCC group showed that IL6 level has no significant correlation with HB ,PLT, WBCS, ESR, RBS, s. albumin, AST, ALT, T. bilirubin. In agreement with a group of researchers who found no correlation between IL6 and serum albumin in HCC

patients (25) In partial agreement to these results.

These results came in disagreement with study conducted by a researcher and his colleagues (15) who demonstrated a positive correlation between serum IL6 and AST but, serum IL6 not correlated with albumin, ALT and total bilirubin, Finally, the exact biological role of this cytokine in liver tumor genesis, growth and progression also warrants more in-depth investigation.

The diagnostic performance of serum IL-6 in HCC and control groups At a cut off value of 25.15, IL-6 showed a sensitivity of 100%, a specificity of 90%, PPV of 97.2, NPV of 100 and AUC=0.931. At a cut off value of 25.15pg/ml for IL-6 and cut off value of 8.1ng/ml for AFP showed a sensitivity of 100%, a specificity of 37.1%, PPV of 61.4%, NPV of 100% and AUC=0.686.

Conclusion

Serum level of IL-6 can represent a potential beneficial biomarker for diagnosis of hepatocellular carcinoma with good sensitivity especially if combined with AFP but with low specificity and may have a limited role in prognosis of hepatocellular carcinoma.

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