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ORIGINAL ARTICLE

Evaluation of Transforming Growth Factor- β 1 in Diagnosis of Hepatocellular Carcinoma in Egyptain HCV Patients

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ABSTRACT

Background and study aim: Transforming growth factor-beta 1 (TGF-β1) is a member of transforming growth factor beta family that acts as a multi-functional cytokine and participates in cellular growth, proliferation and differentiation. This work points to assess the serum level of transforming growth factor-β1 in determination of hepatocellular carcinoma (HCC) in cirrhotic Egyptian patients due to chronic hepatitis C infection (HCV).

patients and methods: 35 cirrhotic patients with HCC, 30 cirrhotic patients without HCC and 20 healthy volunteers were selected in this study. Serum TGF-β1 protein level (pg/ml) by immunoassay was done for all subjects.

Results: a highly statistically significant difference was found between the three studied groups as regard serum level of TGF-β1. TGF-β1 level ≥733.9 (pg/ml) are diagnostic for HCC presence.

Conclusion: Serum level of TGF-β1 may be used as a diagnostic marker for HCC patients.

Key words: Transforming growth factor-beta 1 (TGF-β1), Hepatocellular carcinoma (HCC), Hepatitis C virus (HCV).

INTRODUCTION

Hepatocellular carcinoma (HCC) is the foremost common primary liver cancer which develops in cirrhotic patients. It represents the most common cause of cancer-related Deaths [1]. Most of the HCC cases create within the nearness of cirrhosis related to viral hepatitis. In specific, hepatitis C infection (HCV) and hepatitis B infection (HBV) which are considered major risk factors for HCC around the world, however expanding numbers of HCC in non alcoholic fatty liver diseases (NAFLD) were detected [2]. In Egypt, it is accepted presently that HCC is one of the most common malignancies and a driving cause of passing due to high prevalence of cirrhosis related to chronic HCV. In past a long time, there's an increment in its frequency and it is anticipated that the number of cases proceeds to develop [3]. Early detection remains the main challenge for effective HCC treatment outcome [4]. Patients at high risk are usually assessed by non-invasive imaging tests combined with measurement of serum alpha-fetoprotein (AFP) [5]. However, these assessments could achieve early HCC diagnosis in 30–60 % of the cases in developed countries [6]. Therefore, the identification of other new markers for HCC with high sensitivity and specificity is essential. Transforming growth factor-β1 (TGF-β1) is a well known developmental factor involved in regulation of cell proliferation, differentiation, invasion and inflammation. In mammals, the TGF-β family controls numerous cellular capacities playing a vital part in cell development, separation, apoptosis, extracellular matrix (ECM) generation, immunization and indeed embryonic development [7]. TGF-β1 plays a major part within the pathogenesis of various liver illnesses, such as fibrosis and cirrhosis [8].

Aim of the study:

This study looked at the clinical utility of TGF-1 serum levels in the diagnosis of (HCC) in cirrhotic Egyptian patients.

SUBJECT AND METHODS

This was a case – control study which was carried out on 65 patients and 20 sound volunteers, admitted to the Hepatology, Gastroenterology and Infectious Diseases Department in Benha University Hospital in period from February 2018 to October 2018 in participation with the Medical Biochemistry and Molecular Biology Department. The protocol of

this study was approved by the Ethical Committee of the Faculty of Medicine, Benha University and informed consent was taken from each subject before participation in this study. The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

The subjects were divided as the following:**Group (I):** formed of 20 apparently healthy persons served as a control group.**Group (II):** formed of 30 cirrhotic patients resulting from chronic HCV infection without HCC. **Group (III):** formed 35 cirrhotic patients resulting from chronic HCV infection with HCC.

Patients aged less than 18 years, patients diagnosed with liver cirrhosis (LC) due to other causes than HCV as (HBV infection, autoimmune and metabolic liver diseases), patients with other liver malignancies as (adenoma and hepatoblastoma), patients with metastatic liver cancer, patients with portal vein invasion, patients received prior therapy for HCC lesion, patients with recurrent HCC, patients with past history or on antiviral treatment were not included in this work.

HCC cases were diagnosed by serum α-fetoprotein elevation ≥ 200 ng/dl, abdominal ultrasound and triphasic CT. All subjects were evaluated by thorough full medical history, clinical examination and laboratory investigations.

Sample collection: Venous blood sample (6ml) was taken from each participant under complete aseptic conditions. The blood sample will be divided into 3 parts: the first part (1ml) was put into sterile vaccutainer EDTA tube for CBC. The second part (0.9 ml) was withdrawn into a tube containing tri-sodium citrate (concentration 3.8%) solution in a ratio of 9:1 for determination of PT concentration, activity and INR. The third part (4 ml) was left to clot and serum was separated for other serological and biochemical investigations.

Laboratory investigations were done as follow:Complete blood picture (CBC) performed by automated hematology analyzer Sysmex XS-1000i, **ESR** (ml/hour)**, Random blood glucose** (mg/dl)**,Kidney function tests:** serum creatinine (mg/dl) and blood urea (mg/dl),**Liver profile:**Serum alanine transferase (ALT) and aspartate transeferase (AST) (U/dl), Serum albumin (g/dl), Serum bilirubin (total and direct) (mg/dl), Prothrombin time (PT) (sec), concentration (PC)(%) and international normalized ratio (INR) using Behring Fibrin timer II from (Behring, Germany),**Viral markers:** HCV Abs and HBsAg by third generation of enzyme linked immuno-sorbent assay (ELISA)**, Serum alpha feto-protein level (AFP)** (ng/ml) by ELISA, **Serum TGF- β_1 protein level (pg/ml)** by human TGF- β1 immunoassay (Quantikine ELISA, Minneapolis, USA).

Viral markers and AFP were performed by ***Tecan Infinite spectrophotometer 50 ELIZA Reader (Singapore).*** The other tests were done by ***Microtech spectrophotometer (Vital Scientific, Netherlands).***

Statistical analysis:

The SPSS 12.0 factual program was utilized for factual investigation (Spss Inc, Chicago). Categorical information was displayed as number and rates whereas quantitative information was communicated as cruel ± standard deviation and extend. Chi square test (X2) was utilized to analyze categorical factors, chances proportions (OR) were calculated when pertinent. Quantitative information was tried for ordinariness utilizing Shapiro-Wilks test, accepting typicality at P>0.05. Contrast among 3 autonomous implies was analyzed utilizing examination of fluctuation (ANOVA) for parametric factors or Kruskal Wallis test (KW) for non parametric ones. ROC bend was utilized to decide cut off esteem of the considered markers with ideal affectability and specificity in early conclusion of HCC. Uni and multi variable calculated relapse examination were run to identify the critical indicators of HCC. The acknowledged level of noteworthiness in this work was significant when (P<0.05)

RESULTS

The studied subjects were 85 with no significant differences in age and gender distributions between the cases and controls was found **(Table 1)**. Almost all studied parameters showed significant difference among the studied groups **(Table 2).** However, no statistically significant difference was reported between the studied groups regarding Child-Pugh classification as shown in **(Figure 1).**

The serum level of TG-β1 **(Table 3),** showed highly statistically significant difference between the studied groups (p<0.001 for all). Statistically significant positive correlation of serum level of TGFβ-1 with Child score (rh=0.371, p=0.028) and serum level of AFP (rh=0.533, p=0.001) among HCC group was found **(Table 4),** (**Figure 2)**.

The present study found that, AFP and TGF-β1 can significantly predict HCC at the shown cut off values (≥ 41 ng/ml, ≥ 733.9 pg/ml**)** respectively **(Table 5).**

Regarding univariable binary logistic regression analysis revealed that, age > 58 years, creatinine level > 1.3 (mg/dl), serum albumin

level < 2.5 (g/dl), ESR > 80, AFP ≥ 41(ng/ml) and TGF ≥ 733.9 (pg/ml) were significant risk factors for HCC. Multivariable binary logistic regression analysis showed that AFP ≥ 41 (ng/ml) and TGF ≥ 733.9 (pg/ml) were significant independent predictors of HCC **(Table 6).**

Table (1): Demographic data of the studied groups

Variables		Group I (Control) (n=20)		Group II (Cirrhotic without HCC) (n=30)		Group III (Cirrhotic with HCC) (n=35)		Test &P	P of multiple comparisons
Age (years)	**Mean±SD**	57.2±8.9		57.5±9.0		62.0±8.7		2.79* (0.067) NS	P_1=1.0 P_2=0.16 P_3=0.13
	Range	45-73		40-80		45-80			
		No.	**%**	**No.**	**%**	**No.**	**%**	χ^2	
Sex	**Male**	9	45.0	11	36.7	20	57.1	0.34 0.75 2.71	P_1=0.55 P_2=0.38 P_3=0.099
	Female	11	55.0	19	63.3	15	42.9		

P1: between group I and II, P2: between group I and III, P3: between group II and III

*ANOVA

Table (2): Comparison between the studied groups as regard laboratory findings

Variables	Group I (control) (n=20)		Group II (cirrhotic without HCC) (n=30)		Group III (cirrhotic with HCC) (n=35)		Test & P	P of multiple comparisons
	Mean	**±SD**	**Mean**	**±SD**	**Mean**	**±SD**		
PLTs (c/µl)	272.7	79.1	114.7	76.5	132.1	92.9	24.1 &<0.001 *	P_1<0.001 P_2<0.001 P_3<0.001
S. creatinine (mg/dl)	0.89	0.21	1.10	0.75	1.41	0.79	15.7 &<0.001**	P_1=0.01 P_2=0.001 P_3= 0.024
ESR (ml/hour)	13.5	7.96	53.0	36.2	81.0	38.4	41.2& <0.001**	P_1<0.001 P_2<0.001 P_3<0.001
AST (U/dl)	32.5	12.3	46.6	21.6	54.5	39.9	11.07 &0.004 **	P_1=0.29 P_2=0.027 P_3= 0.85
T. bilirubin (mg/dl)	0.99	0.23	3.6	3.42	3.2	4.54	30.2 & <0.001 **	P_1=0.009 P_2=0.03 P_3=1.0
S. albumin (g/dl)	4.22	.48	2.68	.64	2.63	.55	56.3* &<0.001 *	P_1<0.001 P_2<0.001 P_3<0.001
INR	1.03	0.09	1.43	0.35	1.85	2.31	31.2&<0.001 **	P_1=0.012 P_2=0.003 P_3=0.023
AFP (ng/ml)	1.74	1.48	33.8	32.44	238.7	232.19	56.3 & <0.001 **	P1<0.001 P2<0.001 P3<0.001

P1: between group I and II, P2: between group I and III, P3: between group II and III

*: ANOVA, ** : KW test , SD: standard deviation, PLTs : platelets, S.: serum, ESR : Erythrocyte sedimentation rate, AST: Aspartate transeferase, T.: total, INR : International normalized ratio, AFP : Alpha-feto protein.

Table (3) : Comparison between the studied groups regarding Serum level TGF-β1

Variables	Group I (control) (n=20)		Group II (cirrhotic without HCC) (n=30)		Group III (cirrhotic with HCC) (n=35)		ANOVA & P	P of multiple comparisons
	Mean	±SD	Mean	±SD	Mean	±SD		
Serum level TGF-β_1 (pg/ml)	131.9	59.2	531.5	131.6	1343.2	380.9	158.9 & <0.001 (HS)	P_1<0.001 (HS) P_2<0.001 (HS) P_3<0.001 (HS)

P1: between group I and II, P2: between group I and III, P3: between group II and III
SD: standard deviation

Table (4): Correlation between Serum level TGF-β_1 and the studied variables among HCC group.

	Serum level TGF-B_1 HCC group (N=35)	
	rho	P
Age	-0.165	0.34
FBS (mg/dl)	0.082	0.64
Hb (g/dl)	-0.062	0.72
WBCs (10^3/cmm)	0.183	0.29
PLTs (10^9/L)	-0.103	0.55
S creat (mg/dl)	0.014	0.93
Blood urea (mg/dl)	0.015	0.93
ALT (U/dl)	0.027	0.87
AST (U/dl)	0.146	0.4
T. bilirubin (mg/dl)	-0.179	0.3
D. bilirubin (mg/dl)	-0.182	0.29
S. albumin (g/dl)	-0.182	0.29
ESR (ml/hour)	0.089	0.57
INR	0.164	0.34
AFP (ng/ml)	0.533	=0.001 (HS)
Size	0.23	0.38
MELD	0.139	0.42
CHILD score	0.371	0.028 (S)
OKUDA score	0.168	0.33

FBS: fasting blood sugar, WBC's: White blood cells, PLTs:platelets, ESR: :Erythrocyte sedimentation rate, AFP: Alpha-feto protein , HS:highly significant , s: significant

Table (5): ROC curve analysis for the performance of AFP, serum level of TGF-β1 in the prediction of HCC

Variables	Cut off	Sens%	Spec%	PPV%	NPV%	AUC	95%CI	P
AFP (ng/ml)	≥ 41	82.9%	84%	78.4%	87.5%	0.903	0.83-0.97	**<0.001 (HS)**
Serum level TGF-B_1 (pg/ml)	≥733.9	97.1%	94%	91.9%	97.9%	0.995	0.98-1.0	**<0.001 (HS)**

ROC: receiver operating characteristic, PPV: positive predictive value, NPV: negative predictive value, AUC: area under ROC curve, CI: confidence interval.

Table (6): Multivariable binary logistic regression analysis for the predictors of HCC

Variables	Multivariable logistic regression			
	B	**Adjusted OR**	**95%CI**	**P**
Age >58	13.5	6.1	0.23-35.7	0.91
Loss of weight	16.8	7.0	0.54-49.6	0.86
History of abdominal pain	71.0	12.7	0.89-36	0.76
History of encephalopathy	28.0	5.1	0.49-52.3	0.89
Creat > 1.3 (mg/dl)	10.9	3.8	0.21-24.6	0.96
S albumin< 2.5 (g/dl)	42.1	10.1	0.97-35.8	0.70
ESR > 80 (ml/hour)	83.6	16.4	0.77-44.9	0.67
AFP ≥ 41 (ng/ml)	157.6	29.7	7.5-68.3	**0.004 (S)**
TGF ≥ 733.9 (pg/ml)	165.1	31.2	7.9-99.1	**0.001 (HS)**
Constant	-158.5			

OR: odd ratio, CI: confidence interval , ESR: :Erythrocyte sedimentation rate, AFP: Alpha-feto protein

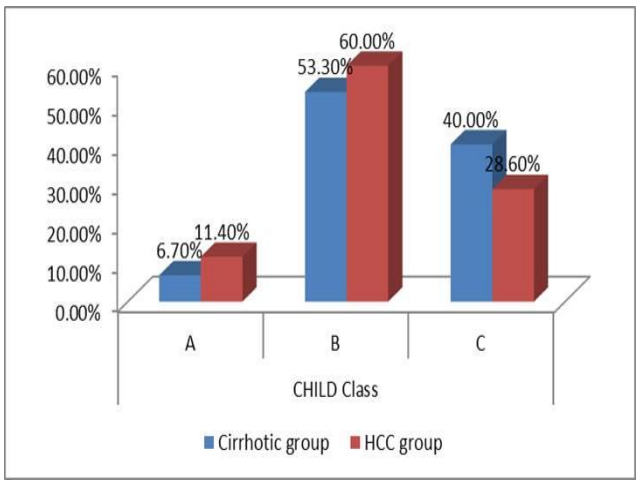

Figure (1) : Bar chart showing Child-pugh classifications among studied patients (cirrhotic with and without HCC).

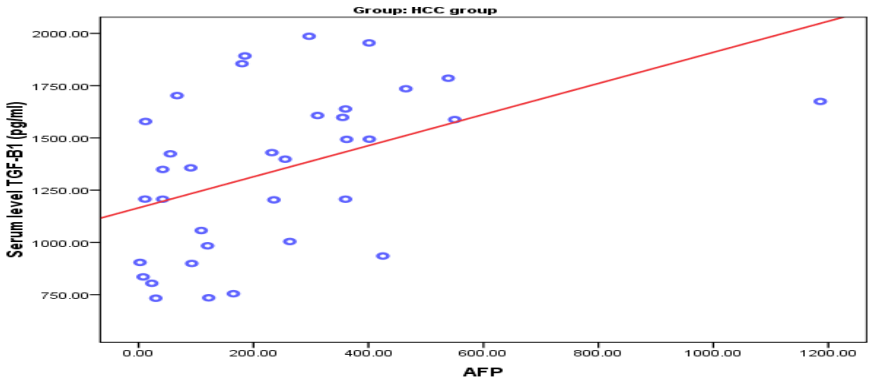

Figure (2) : Scatter graph showing significant positive correlation between AFP and serum level of TGF β1 in HCC group.

DISCUSSION

HCC is considered to be the foremost common essential cancer of the liver. It accounts for 75–85% of essential liver cancers and is the moment driving cause of cancer passing in East Asia and sub-Saharan Africa and the 6th most common in Western [7].

Egypt incorporates a tall rate of HCC approximately 21% in cirrhotic Egyptian patients. HCV and HBV contaminations, diabetes and smoking are the most determinants of HCC advancement in Egypt. There's a synergistic impact of numerous risk factors. A dynamic observation and auxiliary avoidance programs for patients with inveterate hepatitis are the foremost vital steps to decrease the chance of HCC [8].

HCV contamination and its complications are among the driving open wellbeing challenges in Egypt with 13.8% of populace infected , and in these patients, the hazard of HCC is expanded 17-fold [9]. Several ponders that utilize atomic marks have given promising procedure for HCC forecast [10]. So this ponder pointed to evaluate the serum level of TGF-β1 in determination of cirrhotic with HCC Egyptian patients chronically infected with HCV.

In this work, the mean age of patients with HCC was (62.0±8.7 years) (ranging from 45-80 years) without significant difference among HCC and cirrhotic groups (P value =0.13) **(Table 1)**. This result agreed with **El-Sherbiny et al.,** who reported that the age of the HCC patients (ranging from 24 to 83 years) with the mean age of (62.73±10.59 years) [11].. On the other hand, **Tanaka et al.,** reported that the age of HCC incidence was higher in Japan (70–79 years) [12]. This difference may be partially attributed to the difference in the risk factors distribution among Japanese patients with HCC, which was highly variable, depending on geographic region, race or ethnicity.

This current study showed that, HCC is presented more frequently in males than females with male to female ratio (1.33:1) **(Table 1)** with insignificant difference between HCC and other groups**.** This male predominance came in agreement with **Al-sheikh et al.,** who reported that male/female ratio of HCC group was (1.3:1) without significant difference between other groups[13]. .

Several factors may explain males predominance in HCC as males are more likely to be infected with HCV and HBV, in addition to cigarettes smoking and alcohol consumption, testosterone rate has been shown to correlate with HCC indicating a probable role for the sex hormones in the development of HCC [14].

In the current work **(Table 2)**, there was statistically significant difference between HCC and cirrhotic groups regarding platelet count (P<0.001), this result was agreed with **Elgamal et al.,** who reported that there was significant difference between HCC and cirrhotic groups as regard platelet count (P<0.001)(3).

In this work, statistically significant difference was reported as regard serum creatinine level between HCC and control group and between HCC and cirrhotic group (P = 0.001, P = 0.024) respectively **(Table 2)**, and this was agreed with **Omar et al.,** who stated that there was significant difference between HCC group and healthy, chronic hepatitis C and LC as regard serum creatinine level[15]. On the other hand **Elgamal et al.,** documented that, there was no statistically significant difference between HCC group and cirrhotic group as regard serum creatinine level, and this difference may be due to the difference in sample size as the previous study recruited larger number of patients (296 cases of HCC patients and 109 cases of cirrhotic without HCC patients)[3]..

As regard AST level **(Table 2)**, statistically significant difference was found between HCC group and control group (P=0.027) and this result was agreed with **Ma et al.,** who stated that there was significant difference between HCC group and control group as regard AST level (P < 0.05)[16].

Serum level of albumin was lower in HCC group than the other groups with statistically significant difference (P value < 0.001) **(Table 2)** and this result came in agreement with **Hanafy and Abdo,** who reported significant lower level of serum albumin between HCC group and other study groups (P value <0.001) [17].

In the present study, concerning level of INR **(Table 2)**, statistically significant difference was documented between HCC and cirrhotic groups (P=0.023), this result was agreed with **Elgamal et al.,** who reported that, there was significant difference between HCC and cirrhotic groups as regard INR level (P<0.001) [3].

Statistically significant difference in AFP level was reported between HCC group and the other groups (P value < 0.001) **(Table 2)**. This finding agreed with **Metwaly et al.,** who stated that, there was significant difference in AFP level between HCC group in comparison with cirrhotic, chronic hepatitis C and control groups (P value < 0.001) for all [18].

In the present study, most HCC patients were Child B (60%), followed by Child C (28.6%) then Child A (11.4%) with no statistically significant difference **(Figure 2).** Similar results were reported by **El-Sherbiny et al.,** who documented that the majority of HCC patients were Child B (46.25%)(11). On the other hand, **Abu El Makarem et al.,** found that the majority of HCC patients were Child C[19].

In the present work, serum level of TGF-β1 was statistically significantly higher in HCC group compared with cirrhotic and control groups (P value < 0.001) **(Table 3).** This result was agreed with study reported by **Kohla et al.,** who reported significantly higher levels of TGF-β1 in HCC patients compared to the other two groups (cirrhotic and healthy control) (p value =0.000) [20]. On the other hand **Farid et al.,** reported that there was no significant difference between HCC group and liver cirrhosis group as regard serum level of TGF-β1 (P = 0.365), this difference may be due to difference in the sample size which was smaller than our study(20 HCC, 20 LC and 20 healthy volunteers)[21]..

In the current study, positive correlation between serum level of TGF-β1 and AFP in HCC group was found (rh = 533, P = 0.001) **(Table 4)**. On the other side **Farid et al.,** showed no significant correlation between serum TGF-b1 level and AFP in all the studied groups (HCC, LC and healthy control) (rh = - 0.060, P = 0.648). This difference in correlation may be due to difference in the sample size which was smaller than our study (20 HCC, 20 LC and 20 healthy volunteers)(21). Also **Song et al.,** showed that the plasma level of TGF-β1 was not correlated with serum AFP level in patients with small HCC. (r = 0.2; P = 0.21) and also this difference in correlation may be due to difference in ethnicity as this study was conducted on Asian patients or may be due to difference in etiology as it was mixed etiology not pure HCV infection [22]. .

In the current study, positive correlation between serum level of TGF-β1 and Child score in HCC group was reported (rh = 0.371, P = 0.028) **(Table 4).** That was documented by **Kohla et al.,** who stated that serum levels of TGF-β1 were significantly higher with more advanced liver disease assessed by Child Pugh classification (P = 0.035)(20). On the other side **Farid et al.,** showed no significant correlation between serum TGF-b1 level and Child score in all the studied groups (HCC, LC and healthy control) (rh = -0.242, P = 0.133), This difference in correlation may be due to difference in the sample size which was smaller than our study (20 HCC, 20 LC and 20 healthy volunteers) [21].

In the present study, AFP sensitivity and specificity in the prediction of HCC were (82.9% and 84%) respectively **(Table 5)**. **Farid et al.,** reported slightly lower sensitivity and higher specificity of AFP for discrimination between HCC and LC were (65% and 95%) respectively, this difference in sensitivity and specificity may be due to difference in the sample size which was smaller than our study (20 HCC, 20 LC and 20 healthy volunteers) [21]. On the other hand **Kohla et al.,** reported slightly lower sensitivity and much lower specificity (72% and 43%) respectively, this difference in sensitivity and specificity may be due to difference in the selection of patients, as the previous study involved patients with vascular invasion and this was excluded from our study and also may be due to different sample size, as he conducted his study on larger sample size (120 HCC, 30 LC and 30 healthy volunteers) [20].

In this study, the sensitivity and specificity of serum level of TGF-β1 in the prediction of HCC were (97.1% and 94%) respectively **(Table 5)**, that was much higher than **Kohla et al.,** who stated that sensitivity and specificity of serum level of TGF-β1 in the prediction of HCC were (72% and 65%) respectively, this difference in sensitivity and specificity may be due to difference in the selection of patients , as his study involved patients with vascular invasion and this was excluded from our study and also may be due to different sample size , as he conducted his study on larger sample size (120 HCC, 30 LC and 30 healthy volunteers).

In the current study, factors possibly associated with the development of HCC were assessed by univariable regression analysis compared with non HCC groups. These factors included age > 58 years, creatinine level > 1.3 (mg/dl), serum albumin level < 2.5 (g/dl), ESR > 80, AFP ≥ 41 (ng/ml) and serum level of TGF ≥ 733.9 (pg/ml).

This was agreed with **Elgamal et al.,** who documented that, highest risk for development of HCC by binary logistic regression for prediction of HCC cases were age more than 58 years, hypoalbuminaemia and increase level of AFP(3). **Morsy et al.,** documented that age ≥ 50 years correlated with increasing risk of HCC development by univariate analysis of potential risk factors of HCC in cirrhotic patients[22]. Also, **Hedenstierna et al.,** stated that decrease albumin levels remained significantly correlated with HCC development by univariate analysis[23].

In the present work, multivariable binary logistic regression analysis for prediction of HCC revealed that only AFP ≥ 41 (ng/ml), serum level of TGF ≥ 733.9 (pg/ml) were significant independent predictors of HCV- related HCC **(Table 6).**

As for our knowledge, there is no literature discussed these parameters as predictors for HCC but some studies as **Bai et al.,** reported that, AFP level was an independent risk factor associated with tumor differentiation, TNM stage, tumor size, and survival of patients with HCC[24]. Also, **Lee et al.,** discussed that, the serum level of TGF-β1 was a significant independent prognostic factor of HCC [25].

CONCLUSION

Serum level of TGF-β1 may be used as a diagnostic marker for HCC patients.

Abbreviations:

Transforming growth factor-beta1 (TGF-β1)
hepatocellular carcinoma (HCC)
hepatitis C virus (HCV).
hepatitis B virus (HBV)
non alcoholic fatty liver disease (NAFLD)
liver cirrhosis (LC)

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