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Ahmed Shoaib
Menoufia University

Alaa Efat Hasan
Menoufia University, alaaefat@yahoo.com

Elsayed Elshayeb
Menoufia University

Farouk Fouad
Menoufia University

Ibrahim Baghdady
Menoufia University

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Authors

Ahmed Shoaib, Alaa Efat Hasan, Elsayed Elshayeb, Farouk Fouad, Ibrahim Baghdady, Mohammed Sayed, and Yassin Salah

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Ibrahim Baghdady[a], Farouk Fouad[a], Mohammed Sayed[b], Ahmed Shoaib[a], Yassin Salah[a], Elsayed Elshayeb[a], Alaa Efat Hasan[a]

[a]Department of Internal Medicine, Faculty of Medicine, Menoufia University [b]Department of Clinical Pathology, National Liver Institute, Menoufia, Egypt

Correspondence to Alaa Efat Hasan, MSc, Department of Internal Medicine, Faculty of Medicine, Menoufia University, Yassin Abdel-Ghaffar St from Gamal Abd-Elnasser St, Shebin Al-Kom, Menoufia, Egypt
Tel: +20 100 464 3123;
e-mail: alaaefat@yahoo.com

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Objective
The aim of this study was to identify the serum markers and the use of abdominal ultrasound for early detection of hepatocellular carcinoma (HCC) in patients with chronic viral hepatitis C virus infection.

Background
HCC meets the criteria of a tumor that would benefit from a surveillance program, but the poor sensitivity and specificity of currently available tools have prevented widespread implementation of surveillance.

Patients and methods
This study included 110 patients, age from 23 to 70 years, from Menoufia University hospitals during the period from July 2011 to November 2013. They were classified into three groups: group I, non-HCC group (50 patients); group II, HCC group (40 patients with chronic hepatitis C virus infection); and group III, healthy controls (20 individuals). Members of the study were subjected to thorough history taking, complete physical examination, liver function testing (serum bilirubin, albumin, prothrombin time, serum transaminases), serum α-fetoprotein (α-FP), and transforming growth factor β1 (TGF-β1) level. Group I was subjected to serum TGF-β1 at 0-, 9-, and 18-month intervals.

Results
The mean age was 46.72 ± 9.03 years in the non-HCC group (group I), 58.70 ± 5.76 years in the HCC group (group II), and 42.15 ± 11.33 years in the control group (group III). The mean serum level of TGF-β1 was 232.25 ± 70.53 ng/ml in the HCC group, 42.16 ± 13.34 ng/ml in the non-HCC group, and 13.92 ± 7.73 ng/ml in the control group; there was a highly significant difference between all groups ($P < 0.001$). The mean value of α-FP was 334.40 ± 311.30 ng/ml in group II and 4.82 ± 2.18 ng/ml in group I; the HCC group had a shooting serum level of α-FP with a highly statistically significant difference.

Conclusion
This study recommends TGF-β1 as being more accurate than α-FP in differentiating patients with HCC from those with nonmalignant chronic liver disease.

Keywords:
hepatitis C virus, hepatocellular carcinoma, transforming growth factor β1

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Introduction

Hepatocellular carcinoma (HCC) is one of the most common forms of cancer in the world and is the third leading cause of cancer-related death [1].

More than 80% of cases occur in developing countries, and rates are more than twice as high in men. Among primary liver cancers occurring worldwide, HCC is the most common, accounting for 70–85% of liver tumors. In addition, HCC is one of the most fatal cancers, with 5-year relative survival rates of less than 11%, even in developed countries [2].

HCC is multifactorial in origin. These may be divided into major and minor risk factors. Major risk factors include chronic hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, and aflatoxin B1. Minor risk factors include oral steroidal contraceptives and androgens, cigarette smoking, membranous obstruction of the inferior vena cava, and hereditary hemochromatosis [3].

Infection with HBV and/or HCV infections are associated with more than 80% of all HCC cases worldwide [4].

The HCC epidemic in Egypt is associated with HCV infection; up to 90% of the HCC cases in the Egyptian population were attributed to HCV [5].

Two diagnostic tests are routinely used to detect HCC: serum α-fetoprotein (α-FP) and ultrasonography. The sensitivity of α-FP as a diagnostic tool is restricted by the existence of non-α-FP-secreting tumors. The reliability of ultrasonographic diagnosis depends on a

range of factors, including the expertise of the operator, the sophistication of the equipment, and the size and the nature of the tumor [6].

Transforming growth factor β1 (TGF-β1) belongs to a family of homologous, disulfide-linked, homodimeric proteins (five dimeric polypeptides of molecular mass 25 kDa). These highly pleiotropic cytokines inhibit the proliferation of most cells, but can promote the growth of mesenchymal cells and enhance extracellular matrix formation. The pivotal function of TGF-β1 in the immune system is to mediate immunosuppression and maintain tolerance by regulating lymphocyte proliferation, differentiation, and survival. In addition, TGF-β1 controls inflammatory responses through chemotactic attraction and activation of inflammatory cells and fibroblasts. TGF-β1 is produced by many cell types, but is reported to be most abundant in mammalian platelets and bone. It is secreted predominantly as an inactive latent complex. Mature and biologically active TGF-β1 can be released from the complex by the action of proteases and/or conformational changes [7].

TGF-β1 was initially discovered due to its ability to induce fibroblasts to grow in soft agar, a feature associated with oncogenes. Subsequently, TGF-β1 was found to have cytostatic effects on normal nonmalignant cells. These multifunctional effects of TGF-β1 that depend on the cellular context are now well established. In normal cells and in early phases of tumor development, TGF-β1 frequently acts as a tumor suppressor, whereas in the late phases of tumor development, tumor cells become resistant to its antimitogenic effects, and TGF-β1 can switch into a tumor promoter [8].

Patients and methods

This study included 110 participants, age from 23 to 70 years, from inpatient wards and outpatient clinics at Menoufia University hospitals during the period from July 2011 to November 2013. They were classified into three groups: group I (non-HCC group) consisted of 50 patients who did not have HCC and all had chronic HCV infection: they were then subclassified into seven patients with chronic HCV who were HCV positive without cirrhosis, 16 patients with Child–Pugh A, 12 patients with Child–Pugh B, and 15 patients with Child–Pugh C liver cirrhosis. Group II (HCC group) consisted of 40 patients already diagnosed as having HCC by two elements: α-FP higher than the cut-off limit of 200 ng/ml [9], radiological characteristic features of HCC by ultrasound and confirmed by spiral abdominal computed tomography and histopathological features of HCC of liver biopsy performed in 13 patients only with normal α-FP. Group III consisted of 20 age-matched and sex-matched healthy controls.

All studied participants were subjected to the following.

Evaluation of patients

Thorough history was taken from all members of the study groups with special emphasis on symptoms and their duration (e.g. abdominal pain, enlarged abdomen, lower limb edema, etc.). Complete physical examination was performed, with special emphasis on signs of liver cirrhosis, for example, jaundice, pallor, ascites, etc.

Laboratory investigations

All groups were subjected to the estimation of serum bilirubin, albumin and prothrombin time. Also, alanine aminotransferase (ALT) and aspartate aminotransferase (AST), serum α-FP and TGF-β1 (by ELISA technique) were estimated.

Group I was subjected to serum TGF-β1 and α-FP at 0-, 9-, and 18-month intervals.

Specimen collection

Serum

Blood was collected by venipuncture into centrifuge tubes, allowed to clot, and serum was separated by centrifugation at room temperature.

Specimen storage and preparation

Specimens were capped and stored for up to 24 h at 2–8°C before assaying.

Specimens stored for a longer period were frozen only once at -40°C before assay. Thawed samples were inverted several times before testing.

Determination of transforming growth factor β1 serum level

A commercially available kit (DRG TGF-β1 ELISA, EIA-1864) was used for the three groups according to the method described by Kropf *et al.* [10].

α-FP was determined by the ELISA technique, using a commercially available kit (Quorum Ela Kit; Canada) [10].

Radiology

Group I was subjected to abdominal ultrasound at 0-, 9- and 18-month intervals.

Statistical analysis

The statistical package for the social sciences (SPSS, version 20; SPSS Inc., Chicago, Illinois, USA) software computer program was used for analysis of our data. Statistical tests used in this thesis were as follows:

(1) Description of quantitative variables was in the form of mean ± SD.
(2) Description of qualitative variables was by frequency and percentage.
(3) Student's *t*-test of two independent samples was used to compare quantitative variables.
(4) The χ^2-test was used to compare qualitative variables.
(5) The correlation coefficient test (*r*-test) was used to rank different variables against each other either directly or indirectly.

The significance level (*P*-value) was expressed as follows: *P* value more than 0.05, insignificant; *P* value less than 0.05, significant; and *P* value less than 0.001, highly significant.

Results

In this work, 110 persons were included from inpatient wards and outpatient clinics at Menoufia University hospitals during the period from July 2011 to November 2013. The mean ages of the studied groups (Table 1) were as follows: 46.72 ± 9.03 years in the non-HCC group (group I), 58.70 ± 5.76 years in the HCC group (group II), and 42.15 ± 11.33 years in the control group (group III); our results showed highly significant differences between the HCC group and the other two groups ($P < 0.001$).

The mean of serum ALT (Table 2) in the non-HCC group was 36.94 ± 14.73 U/l, which was significantly lower than that in the HCC group (55.60 ± 30.72 U/l) ($P < 0.05$), and the mean in the control group was 22.30 ± 2.25 U/l, which was highly significantly lower than that in the previous two groups. The mean serum AST in the non-HCC group was 36.54 ± 14.31 U/l, which was significantly lower than that in the HCC group (47.55 ± 16.0 U/l) ($P < 0.05$), and the mean in the control group was 20.05 ± 6.26 U/l, which was highly significantly lower than that in the previous two groups.

The serum albumin (Table 2) in the non-HCC group was 3.05 ± 0.82 g/dl, which was significantly higher than that in the HCC group (2.86 ± 0.47 g/dl)

Table 1 Distribution of the studied patients with regard to their characteristics

	N (%)			Test of significance	*P* value
	Non-HCC (*n* = 50)	HCC (*n* = 40)	Controls (*n* = 20)		
Age (years)				*F* = 33.14	<0.001 (I, II–II, III)
Mean ± SD	46.72 ± 9.03	58.70 ± 5.76	42.15 ± 11.33	<0.001	<0.05 (I, III)
Sex					
Male	27 (54.0)	24 (60.0)	10 (50.0)	χ^2 = 0.61	0.734
Female	23 (46.0)	16 (40.0)	10 (50.0)		
Occupation					
House wife	8 (16.0)	8 (20.0)	3 (15.0)	χ^2 = 15.78	0.046
Farmer	7 (14.0)	13 (32.5)	1 (5.0)		
Employee	14 (28.0)	11 (27.5)	9 (45.0)		
Medical staff	7 (14.0)	2 (5.0)	5 (25.0)		
Worker	14 (28.0)	6 (15.0)	2 (10.0)		
Residence					
Urban	20 (40.0)	18 (45.0)	8 (40.0)	χ^2 = 2.31	0.315
Rural	30 (60.0)	22 (55.0)	12 (60.0)		

I, non-HCC; II, HCC; III, controls; HCC, hepatocellular carcinoma; $P < 0.001$, highly significant; $P < 0.05$, significant; $P > 0.05$, not significant.

Table 2 Statistical comparison of liver function tests between the studied groups

	Mean ± SD			Kruskal–Wallis test	*P* value
	Non-HCC (*n* = 50)	HCC (*n* = 40)	Control (*n* = 20)		
ALT (U/l)	36.94 ± 14.73	55.60 ± 30.72	22.30 ± 2.25	45.75 < 0.001	<0.001 (I, III–II, III)<0.05 (I, III)
AST (U/l)	36.54 ± 14.31	47.55 ± 16.0	20.05 ± 6.26	47.04 < 0.001	<0.001 (I, III–II, III)<0.05 (I, II)
Albumin (g/dl)	3.05 ± 0.82	2.86 ± 0.47	4.30 ± 0.32	*F* = 36.36 < 0.001	<0.001 (I, III–II, III)
Bilirubin (mg/dl)	1.18 ± 0.45	2.49 ± 0.82	1.06 ± 0.14	65.56 < 0.001	<0.001 (I, II–I, III)
INR	1.56 ± 0.47	2.51 ± 2.72	1.04 ± 0.06	51.99 < 0.001	<0.001 (I, III)<0.05 (II, III)

I, non-HCC; II, HCC; III, controls; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HCC, hepatocellular carcinoma; INR, international normalized ratio.

($P < 0.05$), and the mean in the control group was 4.30 ± 0.32 g/dl, which was highly significantly different from that in the previous two groups. The serum bilirubin in the non-HCC group was 1.18 ± 0.45 mg/dl, which was highly significantly lower than that in the HCC group (2.49 ± 0.82 mg/dl) ($P<0.001$), and the mean in the control group was 1.06 ± 0.14 mg/dl. The international normalized ratio in the non-HCC group was 1.56 ± 0.47, which was significantly different from that in the HCC group (2.51 ± 2.72) ($P < 0.05$), and the mean in the control group was 1.04 ± 0.06, which was highly significantly lower than that in the HCC group ($P < 0.001$).

The serum level of TGF-β1 (Table 3) was 232.25 ± 70.53 ng/ml in the HCC group and 42.16 ± 13.34 ng/ml in the non-HCC group, and the mean in the control group was 13.92 ± 7.73 ng/ml, showing a highly significant difference with respect to the three groups. The mean serum α-FP was 334.40 ± 311.30 ng/ml in the HCC group, 4.82 ± 2.18 ng/ml in the non-HCC group, and 4.25 ± 2.22 ng/ml in the control group; therefore, only the HCC group had a shooting serum level of α-FP with a highly significant difference.

The serum TGF-β1 (Table 4) shows a highly significant difference ($P < 0.001$) between the follow-up interval measurements at baseline (42.15 ± 13.34 ng/ml), at the 9-month follow-up (43.96 ± 13.26 ng/ml), and at the 18-month follow-up (45.43 ± 13.30 ng/ml).

With regard to α-FP (Table 5), there was no difference at different follow-up points.

Discussion

In many Egyptian regional registries, liver cancer is the first most common cancer in men and the second in women. In the Gharbiah population-based cancer registry, liver cancer represents 12.7% of male cancer patients and 3.4% of female cancer patients [11].

In Egypt, HCV is the main risk factor for HCC, wherein 71% of the HCC cases are positive for anti-HCV antibodies [12]. The Egyptian Ministry of Health estimated that the incidence of HCV infection among Egyptians is 6.9/100 000 persons per year [13]. The incidence of HCC increases progressively with age, although this varies by country. Thus, in high-incidence countries, the mean age at the time of diagnosis is the third decade of life, and in low-incidence countries, it occurs 2–3 decades later [14].

In this study, the age of patients in the HCC group ranged between 42 and 70 years (mean 58.70 ± 5.76 years), which was higher than that in group I in which the age ranged between 23 and 62 years (mean 46.72 ± 9.03 years). There was a highly significant difference between the two groups with regard to the age. This finding was close to that of Hussein *et al.* [15], Hernandez-Castillo *et al.* [16], and Massoud *et al.* [17], who reported that the mean ages among HCC cases were 53.7 ± 10.1, 57.4 ± 8.7, and 55.2 ± 8 years, respectively.

This study, which consisted of 60% male and 40% female patients, was in agreement with a study on the prevalence and epidemiological features of HCC conducted in Egypt, which included 321 HCC patients, and of them 82.55% were male, whereas 17.45% were female [12]. This was also in agreement with Hussein *et al.* [15], who found that the percentage of male patients (75%) was higher than that of female patients (25%). In comparison, in the non-HCC group also the percentage of male patients (54%) was higher than that of the female patients (46%), but no significant difference was found between them. This was in agreement with Hussein *et al.* [15], who revealed that 57.5% of their patients were male and 42.5% were female.

In this study, the serum AST level in the HCC group was higher than that in the non-HCC group, which is statistically significant ($P<0.05$), and this is in agreement with Durazo *et al.* [18] and Lopez *et al.* [19] (the mean value of AST in HCC was 3.5 times the upper limit of normal), and also with Okonkwo *et al.* [20], who found that the serum AST in HCC was 1.39 times the upper limit of normal; the serum ALT level showed a statistically significant difference between the HCC group and the non-HCC group, which was in agreement with Durazo *et al.* [18] and Lopez *et al.* [19].

Table 3 A statistical comparison between the studied patients regarding their serum transforming growth factor β1 and α-fetoprotein levels

	Mean ± SD			Kruskal–Wallis test	*P* value
	Non-HCC (*n* = 50)	HCC (*n* = 40)	Controls (*n* = 20)		
TGF-β1 (ng/ml)	42.16 ± 13.34	232.25 ± 70.53	13.92 ± 7.73	92.90 < 0.001	<0.001 (I, II–I, III–II, III)
α-FP (ng/ml)	4.82 ± 2.18	334.40 ± 311.30	4.25 ± 2.22	75.80 < 0.001	<0.001 (I, II–II, III)

I, non-HCC; II, HCC; III, controls; α-FP, α-fetoprotein; HCC, hepatocellular carcinoma; TGF-β1, transforming growth factor β1.

Table 4 Distribution of each of the studied non-hepatocellular carcinoma patients regarding their follow-up on the serum transforming growth factor β1 level

TGF-β1 (ng/ml)	Baseline	Follow-up	
		9 months	18 months
Non-HCC group (*n* = 50)			
Mean ± SD	42.15 ± 13.34	43.96 ± 13.26	45.43 ± 13.30
Paired *t*-test	–	4.79	5.50
P value	–	<0.001 (HS)	<0.001 (HS)

HCC, hepatocellular carcinoma; HS, highly significant; TGF-β1, transforming growth factor β1.

Table 5 Distribution of each of the studied non-hepatocellular carcinoma patients regarding their follow-up on the serum α-fetoprotein level

α-FP (ng/ml)	Baseline	Follow-up	
		9 months	18 months
Non-HCC group (*n* = 50)			
Mean ± SD	4.82 ± 2.18	5.18 ± 2.15	5.22 ± 2.07
Wilcoxon test	–	0.90	1.42
P value	–	0.366	0.154

α-FP, α-fetoprotein; HCC, hepatocellular carcinoma.

In contrast, Okonkwo *et al*. [20] showed an elevated ALT level in both the HCC and the liver cirrhosis groups, but it was higher in cirrhosis (1.38 and 1.46 times the upper limit of normal, respectively). The elevated aminotransferase value in HCC reflects damage to adjacent hepatocytes as a direct result of tumor growth or damage to more remote liver cells caused by interference with their blood supply or venous drainage. It may also be due to continuing liver cell necrosis in those with concomitant active cirrhosis or chronic active hepatitis [21].

Wen *et al*. [22] reported a stepwise prediction model involving testing for AST or ALT initially, which are simple for clinicians to implement in their daily practice. When routinely collected AST exceeded 25 IU/l, the risk of HCC increased exponentially with an increasing serum level of AST. Because of the increased risks associated with AST or ALT levels of 25 IU/l or higher, such a finding should have triggered further testing for HBV, HCV, or α-FP to yield a more complete picture. The model using transaminases alone had a high prediction power, with an AUC value of 0.912, which was statistically significantly better than those with testing for HBV, HCV, or α-FP alone [22].

According to other liver function tests, serum albumin, bilirubin, and the prothrombin time showed a highly significant difference between the HCC and the non-HCC groups, the bilirubin being higher, the albumin lower, and the prothrombin time more prolonged in the first group; this is in agreement with Durazo *et al*. [18], who stated that HCC patients had higher levels of serum bilirubin (P = 0.0059), international normalized ratio (P < 0.0001), and lower albumin levels (P < 0.0001) compared with non-HCC patients.

Okonkwo *et al*. [20] also found that the mean value of serum albumin in HCC patients was significantly lower than that observed in patients with chronic hepatitis, but it was not significantly different from those with liver cirrhosis. The average serum bilirubin value was four times the upper limit of normal in the HCC patients. In liver cirrhosis, the average bilirubin was 2.8 times the upper limit of normal, and 57.5% of the patients had elevated bilirubin levels. The average bilirubin level was normal in patients with chronic hepatitis.

The level of α-FP 200 ng/ml was considered diagnostic for HCC according to Saini *et al*. [23], who stated that increased serum levels of α-FP 200 ng/ml in a cirrhotic patient at presentation predicts the development of HCC in these patients.

In this work, the α-FP serum level showed a highly significant elevation in HCC patients, and this was in agreement with Hussein *et al*. [15] who showed a significant elevation of serum α-FP in HCC patients. Durazo *et al*. [18] found that the serum level of α-FP was significantly higher in HCC patients than in non-HCC patients (P<0.0001) and also in agreement with Yasmin-Anum *et al*. [24] and El-Tayeh *et al*. [25].

Battaglia *et al*. [26] also found that the mean plasma concentration of α-FP was significantly higher in untreated patients with HCC as compared with patients with chronic liver disease.

In this study, 13 of 40 patients (HCC group) were proven to have HCC by liver biopsy, and showed normal serum α-FP levels, whereas their mean TGF-β1 levels were highly elevated compared with the normal control levels. This finding points towards the importance or the usefulness of TGF-β1 in suspicious cases of HCC with normal levels of serum α-FP. This is in agreement with Song *et al*. [27] who reported the potential use of serum TGF-β1 assay in α-FP-negative HCC and is also in agreement with Hussein *et al*. [15].

Regarding TGF-β1, a highly significant difference was elicited between the two groups. The serum level of TGF-β1 in the non-HCC group was lower than that in the HCC group. This finding was in agreement with El-Tayeh *et al*. [25] who stated that the HCC group had the highest level; Yasmin-Anum *et al*. [24], Sacco *et al*. [28], Kim *et al*. [29], and Shirai *et al*. [30] also reported higher levels of plasma TGF-β1 in

patients with HCC compared with those with chronic hepatitis and cirrhosis. However, Elgendy *et al.* [31] found that the serum TGF-β1 level increased particularly, but insignificantly, in HCC associated with HCV infection.

This was in contrast to Hussein *et al.* [15], who stated that no significant difference was elicited between the two groups.

Bedossa *et al.* [32] and Battaglia *et al.* [26] reported that the understanding for TGF-β1 re-expression by tumor cells is far more complex because TGF-β1 is a negative growth factor inhibiting DNA replication in hepatocytes; on the basis of this inhibitory effect on liver cell growth, it might be expected that TGF-β1 would decrease during carcinogenesis. Sultan *et al.* [33] reported that TGF-β1 expression is markedly decreased in all patients, particularly in HCC associated with HCV in a study on 67 patients.

Kim *et al.* [29] reported that TGF-β1 was not affected by serum ALT levels, the genotype or the serum HCV titer. These findings are in accordance with our results, which showed that TGF-β1 was not correlated to any biochemical parameter in both groups.

The present study revealed that TGF-β1 had a significant difference between all patients with CHC with and without cirrhosis regarding the Child–Pugh scoring system, as it is a multifunctional cytokine that promotes fibrogenesis through the activation of HSCs and the inhibition of hepatocyte proliferation and replication [34]; this was in agreement with Elgendy *et al.* [31] and El-Bassiouny *et al.* [35]. Also, data from El-Bassiouni *et al.* [36] showed a marked simultaneous increase in the expression of TGF-β1, which was strongly correlated with the stage of liver fibrosis, and this is consistent with the findings of Weng *et al.* [37].

Sanz *et al.* [38] suggested that the interruption of TGF-β1 signaling might improve liver fibrosis and stimulate liver regeneration because it may influence the biology of both HSCs and hepatocytes.

Regarding the correlation between the Child–Pugh staging system and the mean α-FP in the non-HCC group, Child–Pugh classes A, B, and C were 3.69 ± 0.45, 2.60 ± 0.12, and 2.21 ± 0.22 ng/ml, respectively, and the difference was insignificant between Child–Pugh classes A, B, and C, which is in contrast to Chen *et al.* [39] who found a relation between the α-FP level and advancing stages of CHC as they showed that high pretreatment α-FP levels were correlated with advanced fibrosis, higher AST, and a lower platelet count. Advanced fibrosis stages (and higher AST levels or low platelet counts) are the most common and consistent with most previous studies [40].

Regarding the correlation between the Child–Pugh staging system and the mean TGF-β1 in the non-HCC group, Child–Pugh classes A, B, and C were 31.41 ± 1.18, 37.92 ± 2.82, and 60.51 ± 7.88 ng/ml, respectively, and the difference was highly significant between Child–Pugh classes A, B, and C, but no significant difference was found between Child–Pugh classes A and B and chronic non-cirrhotic HCV patients. This in agreement with Hussein *et al.* [15] who found that the mean TGF-β1 in Child–Pugh classes A, B, and C were 182.5 ± 121.6, 337.0 ± 131.5, and 344.0 ± 179.1 pg/ml, respectively, and the difference was highly significant between Child–Pugh classes A and C, and also between Child–Pugh classes A and B, but no significant difference was found between Child–Pugh classes B and C.

This was in agreement with Flisiak *et al.* [41] who reported that plasma TGF-β1 was elevated in patients with a high Child–Pugh score and also stated that elevated plasma TGF-β1 levels in patients with chronic liver disease may be mostly caused by a decreased clearance. Mayoral *et al.* [42] found that the TGF-β1 values decreased significantly with progression of liver dysfunction as assessed by the Child–Pugh score.

According to mean serum level of α-FP in the HCC group according to size there was a significant difference between group less than 3 cm (554.56 ± 352.26 ng/ml) and the group of more than 3 cm or more than one focal lesion (187.62 ± 164.91 ng/ml) but the smaller was the higher levels and this was in accordance with Durazo *et al.* [18] who found no significant difference between patients according to changing size ($P < 0.1416$); however, the α-FP level in serum increased with size. Yasmin-Anum *et al.* [24] demonstrated that the serum level of TGF-β1 was a more sensitive indicator of small HCC than α-FP.

Conclusion

HCC meets the criteria of a tumor that would benefit from a surveillance program, but the poor sensitivity and specificity of currently available tools has prevented widespread implementation of HCC surveillance.

The TGF-β1 is more accurate than α-FP in differentiating patients with HCC from those with nonmalignant chronic liver disease.

Therefore, TGF-β1 was proven to be a candidate as a tumor marker. However, a limitation of this study

was its smaller sample size, and further larger patient studies should be performed to assess the diagnostic value of TGF-β1 in patients with HCC.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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