Diagnostic value of Protein Induced by Vitamin K Absence or Antagonist - II (PIVIKA – II) in patients with hepatocellular carcinoma (HCC): Comparison with alpha fetoprotein

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Abstract: Cirrhosis from any cause predisposes to hepatocellular carcinoma (HCC). An effective surveillance strategy for HCC should be used in high risk populations, including cirrhotic patients, chronic hepatitis C and B to allow early diagnosis. Ultrasound surveillance, as it is currently practiced, has an acceptable sensitivity of 65%-80% and has an upper level of specificity of more than 90%. Combining ultrasound and alpha foetoprotein (AFP) appears to improve detection rates, but also increases costs and the rate of false positives. One of the most useful biomarkers is the abnormal prothrombin, des-gamma-carboxy prothrombin (DCP) or protein induced by vitamin K absence or antagonist II (PIVKA-II), which is an inactive prothrombin deficient in gamma carboxyglutamic acid. It is produced by malignant hepatocytes and may be used as a reliable marker for the diagnosis of HCC. ***Objective:*** The aim of this study is to assess the diagnostic value of protein induced by vitamin k absence or antagonist II (PIVIKA II) in patients with HCC. ***Subjects & Methods:*** This study was carried out on 53 subjects. Subjects were divided into four groups: **Group I:** 15 cirrhotic patients with newly diagnosed HCC with unequivocal diagnostic AFP level (>400ng/ml). **Group II:** 20 cirrhotic patients with newly-diagnosed HCC with normal AFP. **Group III:** 8 patients with established cirrhosis. **Group IV:** 10 healthy volunteers serving as a control group. Patients with non-established cirrhosis, patients with metastatic liver disease, and patients with non-viral chronic liver disease were excluded from the study. All patients were subjected to thorough history taking, complete clinical examination & routine investigations including full blood count, blood glucose, urine analysis, liver enzymes (ALT & AST), serum albumin, serum bilirubin, INR, and viral markers including HBsAg, anti-HCV antibodies, and HCV RNA whenever available. Samples for AFP & Protein induced by vitamin K absence or antagonist II (PIVIKA II) or des gamma carboxy Prothrombin (DCP) were withdrawn. All subjects in the study were also subjected to imaging studies including real time U/S & triphasic Computed tomography (CT) . Percutaneous liver biopsy was done in some cases. ***Results:*** No significant difference was observed between the studied groups regarding gender ($p > 0.05$). Regarding age, statistically significant difference was observed when the 3 groups of patients were compared to the control group ($p < 0.05$). The mean ages of the patients in studied groups were 39.24±11.25, 54.66±7.48, 56.5±6.7 and 53±7.83 years in control group, groups I, II and III respectively. No significant difference was observed between the studied groups regarding Child Pugh staging system. A highly significant difference in the median of serum level of AFP was observed when group I was compared to the control group, group II and group III ($P<0.05$). While no significant difference was observed when median of serum level of AFP in groups II ,III and control were compared to each other ($P>0.05$). Results of our study showed that, at cutoff value of 39 ng/ml, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of AFP as a tumor marker for detection of HCC were 57.6%, 88.9%, 95%, 36.4% and 0.741 respectively. in this study at a cutoff value of 31 ng/ml the sensitivity, specificity, PPV, NPV and accuracy of PIVKA –II as a tumor biomarker for detection of HCC was 79.4%, 88.9%, 53.3% and 0.884 respectively. Receiver-operator characteristic curve (ROC) was plotted to identify cutoff values that would best distinguish HCC from other chronic liver disease. The optimal cutoff values for PIVKA –II and AFP were 31 ng/ml and 39 ng/ml respectively. These values yielded a sensitivity and specificity for PIVKA –II of 79.4%, 88.9% and for AFP of 57.6%, 88.9% respectively. Therefore, the ROC curve indicated a better sensitivity and specificity for PIVKA-II than AFP in differentiating patients with HCC from those with cirrhosis. ***Conclusion:*** The results of the present study clearly demonstrate that PIVKA-II has a better sensitivity and specificity than AFP in differentiating patients with HCC from those with cirrhosis. PIVKA-II should be used as an early reliable biomarker for HCC in risky groups.

[Gamal F. El Naggar , Eman A. Alzamarany. **Diagnostic value of Protein Induced by Vitamin K Absence or Antagonist - II (PIVIKA – II) in patients with hepatocellular carcinoma (HCC): Comparison with alpha fetoprotein**. *J Am Sci* 2012;8(8):1062-1071]. (ISSN: 1545-1003). http://www.jofamericanscience.org. 157

Keywords: Protein Induced by Vitamin K Absence or Antagonist - II (PIVIKA – II), hepatocellular carcinoma (HCC), alpha fetoprotein (ALF).

1. Introduction

Cirrhosis from any cause predisposes to hepatocellular carcinoma (HCC). However, the primary etiology of most cases of HCC is hepatitis C virus (HCV) and hepatitis B virus (HBV) related cirrhosis. HCC represent nowadays the major cause of liver-related deaths (up to 80%) among cirrhotic patients (1). To date, curative treatment options for HCC include orthotopic liver transplantation or surgical resection. Most patients are detected with non-resectable or transplantable HCC due to disease extension, and are therefore candidates for palliative treatments only (2). The only hope for a cure lies in early diagnosis; so, an effective surveillance strategy should be used in high risk populations, including cirrhotic patients, chronic hepatitis C and B (3).

Alpha – fetoprotein (AFP) is a widely used HCC screening test (4,5). The adult value is up to 20ng/ml, progressive increases are found in some patients with HCC, raised levels at presentation in a cirrhotic patient predict development of HCC at follow-up (6). A level more than 400ng/ml is usually regarded as diagnostic (5,7). However, screening for HCC using AFP alone has several limitations. AFP is not elevated in all patients with HCC. Some patients with cirrhosis and/or hepatic inflammation can have an elevated AFP, even without the presence of a tumor (7). In addition, two thirds of HCCs less than 4cm have AFP levels less than 200 ng/ml and up to 20% of HCC do not produce AFP, even when very large. False positives levels in the range of 20-250 ng/ml are frequently seen in regenerating nodules in viral cirrhosis (5).

Ultrasound surveillance, as it is currently practiced, has an acceptable sensitivity of 65%-80% and has an upper level of specificity of more than 90%. Tumor size significantly affects the sensitivity of US in detecting HCC. Sensitivity ranges from 42% for lesions smaller than 1 cm to 95% for tumors of larger size. However, it is often difficult to distinguish HCC from other conditions, as hemangioma and regeneration nodules in patients with cirrhosis (8).

Combining ultrasound and AFP appears to improve detection rates, but also increases costs and the rate of false positives. However, the combination of AFP and U/S as screening tools is not generally used in many countries because the sensitivity of U/S in detecting minute HCCs (<3cm) is high, 80% of new solid nodules detected by U/S are malignant, the sensitivity and positive predictive value of AFP are very low for minute HCCs , and additional AFP testing increases direct and indirect costs of screening (9).

One of the most useful biomarkers is abnormal prothrombin, des-gamma-carboxy prothrombin (DCP) or protein induced by vitamin K absence or antagonist II (PIVKA-II), which is an inactive prothrombin deficient in gamma carboxyglutamic acid and is produced by malignant hepatocytes (10).

Serum PIVKAII has attracted attention because of its very high specificity and lack of correlation with serum AFP levels. Many studies on the relationship between the serum DCP level and various clinicopathological features of HCC have suggested that elevation of DCP reflects worse tumor behavior and prognosis for HCC patients (11). Furthermore, several studies showed that elevated serum level of DCP is significantly related to portal vein invasion and may be an independent prognostic factor (12) .

2. Subjects and Methods:

This study was carried out on 53 subjects. They were recruited from inpatients and outpatients clinic in Internal Medicine Department of Tanta University Hospitals in the period from September 2010 to March 2011. Written informed consent from every subject was taken. Subjects were divided into four groups: Group I: 15 cirrhotic patients with newly diagnosed HCC with unequivocal diagnostic AFP level (>400ng/ml). Group II: 20 cirrhotic patients with newly-diagnosed HCC with normal AFP. Group III: 8 patients with established cirrhosis. Group IV: 10 healthy volunteers serving as a control group. Patients with non-established cirrhosis, patients with metastatic liver disease, and patients with non-viral chronic liver disease were excluded from the study.

All patients were subjected to thorough history taking, complete clinical examination & routine investigations including full blood count, blood glucose, urine analysis, liver enzymes (ALT & AST), serum albumin, serum bilirubin, INR, and viral markers including HBsAg, Anti-HCV antibodies, and HCV RNA whenever available. Samples for Alpha-fetoprotein (AFP) & Protein induced by vitamin K absence or antagonist II (PIVIKA II) or des gamma carboxy Prothrombin (DCP) were withdrawn. PIVIKA II level was assessed by Asserachrom PIVIKA II Kit (diagnostica Stago-France). PIVIKA II concentration in a normal population was found below 2 ng/ml (according to the manufacturer's instructions). All subjects in the study were also subjected to imaging studies including real time U/S & triphasic Computed tomographt (CT) for assessment of: 1-liver, as regards size, texture, reflectivity, homogenicity, hepatic veins. 2-Focal lesions as regards number, site, size, shape, echogenicity, and neovascularization by colour Doppler assessment. 3-Portal vein as regards diameter, patency, direction of flow, respiratory

variation, and velocity by colour Doppler assessment. 4-Spleen, ascites, lymph nodes for extrahepatic spread, portal hypertension & superior mesenteric vein patency. Percutaneous liver biopsy was done in some cases.

Statistical presentation and analysis of the present study was conducted, using the mean, ROC curve, linear correlation coefficient, Chi-square, and Analysis of variance [ANOVA] tests by SPSS V17. The significance level was set at $p < 0.05$.

3. Results:

Group I included 14 male patients (93.33%) and one female patient (6.67%) while *group II* included 18 male patients (90%) and 2 female patients (10%). *Group (III)* included 7 male patients (87.5%) and 1 female patient (12.5%). No significant difference was observed between the studied groups regarding gender ($p > 0.05$). Regarding age, statistically significant difference was observed when the 3 groups of patients were compared to the control group ($p < 0.05$). The mean of age of the patients in studied groups was 39.24±11.25, 54.66±7.48, 56.5±6.7 and 53±7.83 years in control group, groups I, II and III respectively (Table 1).

Total number of Child A in the studied groups was 16 patients (37.2%). They were distributed as 5, 9 and 2 patients in groups I, II, and III respectively. While total number of Child B was 12 patients (27. 9%) . They were distributed as 2, 6, and 4 patients in groups I, II, and III respectively. Total number of Child C was 15 patients (34.9%). They were distributed as 8, 5 and 2 patients in groups I, II, and III respectively. No significant difference was observed between the studied groups regarding Child Pugh staging system ($p > 0.05$) (Table 2).

Hepatic Focal Lesions (HFLs) were detected by U/S in (14/15) patients (93.3%) in group I and in all patients in group II (20) patients (100%). While in group III, no focal lesions were detected at this time. When patients in group I and group II were compared to those in group III, a highly significant difference was detected ($p<0.05$). But no significant difference was observed when patients in group I and group II were compared to each other (Table 3). HFLs were detected by C/T in all patients (15/15) (100%) in group I and in all patients in group II (20) patients (100%). The difference between the studied groups was statistically insignificant ($P>0.05$) (Table 4).

Normal sized cirrhotic liver was detected in 7 patients; enlarged cirrhotic liver was detected in 24 patients, while shrunken cirrhotic liver was detected in 12 patients in the studied groups. Portal vein thrombosis (PVT) was detected in 14 patients in the studied groups . Mild enlargement of the spleen (13 - 16cm) was detected in 15 patients, moderately enlarged spleen (16-19cm) was detected in 16 patients and markedly enlarged spleen (>19cm) was detected in 12 patients in the studied groups. Ascites was detected in 24 patients in the studied groups. As regards the abdominal U/S findings, there was no significant statistical difference between the studied groups except at the point of PVT which showed a significant difference between the studied groups ($p<0.05$) (Table 5).

Regarding site of the HFLs, the imaging modalities detected the focal lesions in the right lobe of the liver in 25 patients, 8 patients in the left lobe and 2 patients in both lobes of the liver . Regarding size of the HFLs the HFL was <3cm in 5 patients, while HFL >3cm was detected in 30 patients in the studied groups. Regarding number of HFLs single focal lesion in 18 patients, two focal lesion was detected in 4 patients and multiple focal lesion in 13 patients of the studied groups. The difference between the studied groups was statistically insignificant ($p>0.05$) (Tables 6, 7, and 8).

The range of serum level of AFP in the control group was (0.9:2.00 ng /ml), median (1.500 ng /ml) while the range serum level of AFP was (426:80000.00 ng /ml), median (1200.000 ng /ml), (0.0100:150.000 ng/ ml), median (18.90 ng /ml) and (3.400:39.000 ng /ml), median (8.85 ng /ml) in groups I, II and III respectively. Therefore, a highly significant difference in the median of serum level of AFP was observed when group I was compared to the control group, groups II and III ($P<0.05$). While no significant difference was observed when median of serum level of AFP in group II , group III and control were compared to each other ($P>0.05$) (Table 9).

The range of serum level of PIVIKA II in the control group was (0.18:1.50 ng/ml), median (1.500 ng /ml) while the range serum level of PIVIKA II was (1.90 :360.00 ng/ml), median (220.00 ng /ml), (1.50:310.00 ng /ml), median(184.50 ng/ml) and (1.00:31.00 ng /ml) , median (1.70 ng /ml) in groups I , II and group III respectively. Therefore, a highly significant difference in the median of serum level of PIVIKA II was observed when groups I and II (HCC patients) were compared to the control group and group III ($P<0.05$). While no significant difference was observed when median value in patients with HCC (group I and group II) are compared to each other ($P>0.05$) (Table 10).

The median serum AFP in single focal lesion was 54.25ng/ml, in two focal lesions was 610.35 ng /ml and in multiple focal lesions was 426 ng /ml. While the median serum PIVIKA II in single focal lesion was 145, in two focal lesions was 233 and in multiple focals lesion was 182. Statistically no significant difference was observed in the studied

groups between serum level of AFP, PIVIKA II and number of the focal lesion (p>0.05) (Table 11).

The median serum AFP in the focal lesion < 2cm was 245.5ng/ml and in the focal lesion > 2cm was 55ng/ml. While the mean serum PIVIKAII in the focal lesion < 2cm was 167.5ng/ml and in the focal lesion >2cm was 191 ng /ml. Statistically no significant difference was observed in the studied groups between serum level of AFP, PIVIKA II and size of the focal lesion (p>0.05) (Table 12).

The median value of serum AFP in patients with portal vein thrombosis was 500 ng/ml and in patients without portal vein thrombosis was 25.7ng/ml. The median serum PIVIKA II in patients with portal vein thrombosis was 170 ng/ml and in patients without portal vein thrombosis was 120 ng/ml. Statistically no significant difference was observed in the studied groups between serum level of AFP , PIVIKA II and portal vein thrombosis (p>0.05) (Table 13).

As regards AFP, at high level cut-off value which are elicited from the Receiver Characteristic Curve (ROC) (Curve I), the high sensitivity was 57.6 % at cut-off value > 39ng/ml while specificity 88.9% with accuracy 74%, PPV 95 and NPV 34.6 (Table 14 & Figure 1). But PVICA-II, at high level cut-off value which are elicited from the Receiver Characteristic Curve (ROC) (Curve II), the high sensitivity was 79.4 % at cut-off value >31ng/ml while specificity 88.9% with accuracy 88.4% , PPV 96.4 and NPV 53.3 (Table 15 & Figure 2).

Table 1: Age distribution in the studied groups.

	Age		ANOVA	
	Range	Mean ± SD	f	*P*-value
Control	28.0 - 56.0	39.200 ± 11.256	6.954	0.001*
Group I	44.0 - 65.0	54.667 ± 7.480		
Group II	40.0 - 66.0	56.500 ± 6.740		
Group III	44.0 - 67.0	53.000 ± 7.838		

Tukey's test					
Control & G I	**Control & G II**	**Control & G III**	**G I & G II**	**G I & G III**	**G II & G III**
0.002*	<0.001*	0.015*	0.896	0.959	0.696

Table 2:-Child Pugh classification of the studied groups

Child		**Groups**			
		Group I	**Group II**	**Group III**	**Total**
Class A	N	5	9	2	16
	%	33.333	45	25	37.2
Class B	N	2	6	4	12
	%	13.333	30	50	27.9
Class C	N	8	5	2	15
	%	53.333	25	25	34.9
Total	N	15	20	8	43
	%	100.00	100.00	100.00	100.00
Chi-square	X^2	5.527			
	P-value	0.2373			

Table 3: Ability of U/ S to detect the focal lesions in the studied groups .

U/S		**Groups**			
		Group I	**Group II**	**Group III**	**Total**
Negative	N	1	0	8	9
	%	6.67	0.00	100.00	20.93
Positive	N	14	20	0	34
	%	93.33	100.00	0.00	79.07
Total	N	15	20	8	43
	%	100.00	100.00	100.00	100.00
Chi-square	X^2	37.360		*P*-value <0.001*	

Table 4: Ability of CT to detect the focal lesions in the studied groups.

CT		Group I	Group II	Total
Negative	N	0	0	0
	%	0.00	0.00	0.00
Positive	N	15	20	35
	%	100.00	100.00	100.00
Total	N	15	20	35
	%	100.00	100.00	100.00
Chi-square	X^2	0.00s		
	P-value	1.000		

Table 5 : U/S finding in the studied groups.

	Group I	Group II	Group III	Total
Liver size				
Normal	4	2	1	7
Enlarged	8	12	4	24
Shrunken	3	6	3	12
PVT				
Absent	7	14	8	29
Present	8	6	0	14
Splenomegaly .				
Mild	8	6	1	15
Moderate	3	10	3	16
Marked	4	4	4	12
Ascites				
Present	9	13	2	24
Absent	6	7	6	19

Table 6: Site distribution of the focal lesion in HCC groups .

Site of HFL		Groups		
		Group I	Group II	Total
Rt. Lobe	N	11	14	25
	%	73.33	70.00	
Lt. Lobe	N	3	5	8
	%	20.00	25.00	
Both.Lobes	N	1	1	2
	%	6.67	5.00	
Total	N	15	20	35
	%	100.00	100.00	100.00
Chi-square	X^2	0.149		
	P-value	0.9283		

Table 7: Number distribution of the focal lesion in HCC groups.

F L		Groups		
		Group I	Group II	Total
Single	N	6	12	18
	%	40.00	60.00	51.43
Two	N	2	2	4
	%	13.33	10.00	11.43
Multi	N	7	6	13
	%	46.67	30.00	37.14
Total	N	15	20	35
	%	100.00	100.00	100.00
Chi-square	X^2	1.391		
	P-value	0.499		

Table8: Size distribution of the focal lesion in HCC groups.

FL		Groups		
		Group I	Group II	Total
<3cm	N	3	2	5
	%	20.00	10.00	
>3cm	N	12	18	30
	%	80.00	90.00	
Total	N	15	20	35
	%	100.00	100.00	100.00
Chi-square	X^2	0.260		
	P-value	0.6098		

Table 9: Comparison between the studied groups as regards range and mean of serum level of AFP (ng/ml).

Group		AFP (ng/ml)		
		Range	Median	Mean rank
Control		0.900 - 2.000	1.500	4.000
Group I		426.000 - 80000.000	1200.000	41.000
Group II		0.100 - 150.000	18.900	20.675
Group III		3.400 - 39.000	8.850	15.938
Kruskal-Wallis Test	X^2	36.057		
	***P*-value**	<0.001*		

Table 10: Comparison between the studied groups as regards range and median of serum PIVKA II.

Group		PIVKA II (ng/ml)		
		Range	Median	Mean rank
Control		0.18 - 1.50	1.50	5.70
Group I		1.90 - 360.00	220.00	32.83
Group II		1.50 - 310.00	184.50	28.52
Group III		1.00 - 31.00	1.70	10.56
Kruskal-Wallis Test	X^2	23.930		
	***P*-value**	<0.001*		

Table 11: Correlation between serum PIVKA II ,AFP and number of the focal lesion.

No of FL		Range	Median	Mean rank	Kruskal-Wallis Test X^2	P-value
AFP	1	0.1 - 10000	54.25	17.25	1.140	0.565
	2	9.1 - 20020	610.35	21.25		
	M	2.8 - 80000	426	21		
PIVKA II	1	1.5 - 321	145	18.075	0.877	0.645
	2	6 - 360	233	23.625		
	M	1.9 - 280	182	19		

Table 12: Correlation between serum PIVKA II ,AFP and the size of the focal lesion.

Size of FL		Range	Median	Mean rank	Mann-Whitney Test Z	*P*-value
AFP	<2cm	4.15 - 10000	245.5	19.25	-0.062	0.951
	>2cm	0.1 - 80000	55	18.95161		
PIVKA	<2cm	6 - 276	167.5	16.66667	-0.577	0.564
	>2cm	1.5 - 360	191	19.45161		

Table 13: Correlation between serum PIVKA II, AFP and portal vein thrombosis.

PVT		Range	Median	Mean rank	Mann-Whitney Test Z	*P*-value
AFP	Absent	0.1 - 10000	25.7	19.44828	-1.619	0.105
	Present	8.7 - 80000	500	26.07692		
PIVKA	Absent	1 - 320	120	20.67241	-0.653	0.514
	Present	1.9 - 360	170	23.34615		

Table 14: The sensitivity ,specificity and predictive values of AFP at cutoff level of (39 ng/ml) in diagnosis of HCC.

ROC curve between imaging studies and AFP(ng/ml)					
Cutoff	Sens.	Spec.	PPV	NPV	Accuracy
> 39	57.6	88.9	95.0	36.4	0.741

Table 15: The sensitivity ,specificity and predictive values of PIVKA-II at cutoff level of (31ng/ml) in diagnosis of HCC.

ROC curve between imaging studies and PIVKA(ng/ml)					
Cutoff	Sens.	Spec.	PPV	NPV	Accuracy
> 31	79.4	88.9	96.4	53.3	0.884

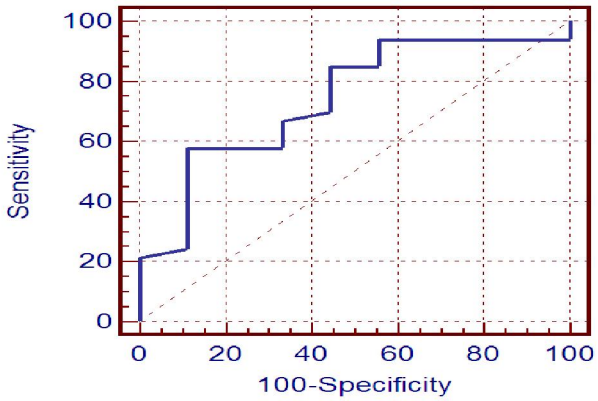

Figure 1: Curve I: The Receiver Operator Characteristic (ROC)Curve for detecting the sensitivity and specificity of AFP.

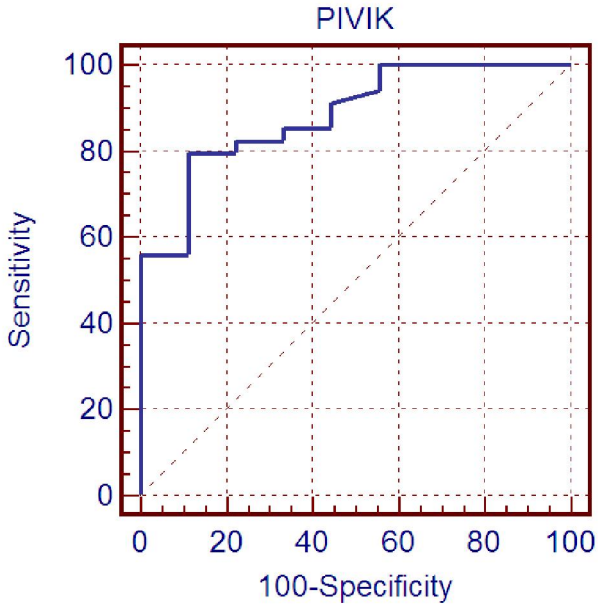

Figure 2: Curve II :The Receiver Operator Characteristic (ROC)Curve for detecting the sensitivity and specificity of PIVKA II.

4. Discussion:

This study was conducted to evaluate the sensitivity and specificity of PIVIKA-II in diagnosis of HCC among a group of our Egyptian patients as compared to AFP. Results of our study showed that, at cutoff value of 39 ng/ml, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of AFP as a tumor marker for detection of HCC were 57.6%, 88.9%, 95%, 36.4% and 0.741 respectively.

Protein induced by vitamin K absence (PIVKA II) is secreted by hepatoma cells and used widely in Japan and United States as a sensitive marker for diagnosis of HCC since 1998. Its diagnostic accuracy has been investigated in multiple studies with conflicting results (13). *In the present study,* the mean value of serum PIVKA –II was 220 ng /ml$\pm$184.5 in HCC patients in group I and group II respectively , while it was 1.7 ng/ml and 1.5 ng/ml in group III (cirrhotic patients without HCC) and group IV (control group) respectively . The increased level of PIVKA –II in the cirrhotic HCC patients (groups I, II) was statistically significant when both groups are

compared to the cirrhotic patients and the control group (G III and G IV).

Based on these findings, in this study at a cutoff value of 31 ng/ml the sensitivity, specificity, PPV, NPV and accuracy of PIVKA –II as a tumor bio marker for detection of HCC was 79.4%, 88.9%, 53.3% and 0.884 respectively. Receiver-operator characteristic curve (ROC) was plotted to identify cutoff values that would best distinguish HCC from other chronic liver disease. The optimal cutoff values for PIVKA –II and AFP were 31 ng/ml and 39 ng/ml respectively. These values yielded a sensitivity and specificity for PIVKA –II of 79.4%, 88.9% and for AFP of 57.6%, 88.9% respectively. Therefore, the ROC curve indicated a better sensitivity and specificity for PIVKA-II than AFP in differentiating patients with HCC from those with cirrhosis . **Marrero *et al.*(2003)** found that at a cutoff value of 125 mAU/mL, DCP was superior to AFP in the diagnosis of HCC regardless of the AFP value chosen (14). This DCP value is higher than values used in studies from Asia (40-100 mAU/mL) (15, 16). In contrast to our results, another Japanese study conducted by **Volk *et al.* (2007)**, reported that the performance of PIVKA-II was rather lower than AFP ,the AUROC of each marker was 0.812 and 0.887, respectively (17).

Regarding the prognostic value of tumor markers, in our study, no significant correlation was found between PIVKA –II level and the size, number of tumors or PVT in our study. *Review of relevant publications reveled that*, also other studies found no correlation between AFP and PIVKA –II levels and tumor characteristics (size &number of FL) as well as PVT (14). By contrast, several other studies have demonstrated a significant correlation between higher serum level of PIVKA –II and tumor characteristics (size & number of HFL) as well as PVT (18, 19).

It is noteworthy to mention that, in our study no significant correlation was found between serum level of tumor markers (AFP &PIVKA –II) and the Child class in our cirrhotic patients with HCC ,denoting that these markers are not affected by the severity of underlying liver disease.

DCP plays several important roles in HCC progression and may explain why cancer behaviour and patient prognosis worsen in patients with DCP-positive HCC in comparison with those with DCP-negative HCC. DCP is not just an abnormal prothrombin but may be a potential cancer enhancing protein. (13).

Conclusion& Recommendations :

The results of the present study clearly demonstrate that, PIVKA-II has a better sensitivity and specificity than AFP in differentiating patients with HCC from those with cirrhosis. PIVKA-II should be used as an early reliable biomarker for HCC in at risk groups.

We recommend a large scale multicenter studies covering the different Egyptian population to better clarify the diagnostic performance of this new biomarker among our Egyptian patients whether alone or in combination with AFP. Further studies are needed to elucidate the role of DCP, not only as a biomarker, but as a therapeutic target for HCC.

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9/25/2012