Evaluation of Pivka-II as a Predictor Marker for Portal Vein Obstruction in Hepatocellular Carcinoma Patients

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Abstract: Background: Hepatocellular carcinoma (HCC) is the sixth most common malignancy and the third most common cause of cancer-related death worldwide. While the survival of patients with most malignancies has improved over the last decade, 5-year survival of patients with HCC has remained less than 10% . Presence of portal vein thrombosis hinders prognosis and limits therapeutic options of management in HCC. Des-gamma carboxyprothrombin (DCP), also known as protein induced by vitamin K absence/antagonist-II (PIVKA-II), is an abnormal form of the coagulation protein, prothrombin . Aim: The aim of our study was to evaluate the value of PIVKA-II measurement as a predictor of portal vein obstruction among other factors when HCC on liver cirrhosis is diagnosed with trans-abdominal ultrasound. Patients and Methods: The present study included fifty newly diagnosed patients (37 males and 13females) with proved histopathological diagnosis of HCC who were diagnosed at Hepatology Unit at Ain Shams University hospital. Patients were subjected to history taking, physical examination and radiological assessment with abdominal ultrasonography and computerized tomography. The following laboratory investigations were done, -Complete blood picture (CBC), Prothrombin time (PT) and international normalized ratio (INR).,Liver function tests (ALT, AST, ALP, serum albumin and serum bilirubin) :,Kidney function tests (serum creatinine).,Alpha feto protein (AFP) determination).and Serum PIVKA-II level determination using micro cup type enzyme immunoassay test kit Results: In the present study, a statistically higher PIVKA-II (z=2.575; p=0.010) has been found in patients with PVT on comparison with patients without PVT. PIVKA-II levels were 97.0mAu/ml±81.3 , with a range from 0.8 to 266.3 for patients with PVT and 40.2 mAu/ml±40.6), with a range from 0.2 to 146.3 for patients without PVT In conclusion serum PIVKA II levels >100mAu/ml is a predictor for development of PVT in patients with HCC and which influences the therapeutic options available for the patients.
[Kalid Hemida, Wafaa kamal, George S. Riad, Nanees A.Adel and Maryse S.Ayoub,Dena Fekry. **Evaluation of Pivka-II as a Predictor Marker for Portal Vein Obstruction in Hepatocellular Carcinoma Patients.** *J Am Sci* 2012;8(11):162-170]. (ISSN: 1545-1003). http://www.jofamericanscience.org. 23

Keywords: PIVKA II,Hepatocellular carcinoma,portal vein obstruction.

1. Introduction

Hepatocellular carcinoma (HCC) is the sixth most common malignancy and the third most common cause of cancer-related death worldwide **(Kamangar *et al.*, 2006)**. While the survival of patients with most malignancies has improved over the last decade, 5-years survival of patients with HCC has remained less than 10% **(Everhart, 2008)**. The poor outcome of patients with HCC is related to the late detection with more than two-thirds of patients diagnosed at advanced stages of disease **(Stravitz *et al.*, 2008)**. Cirrhosis of any cause and chronic infection with hepatitis B virus (HBV) or hepatitis C virus (HCV) are the most common risk factors for HCC surveillance **(Bruix and Sherman, 2005)**.

In Egypt, extensive research over the past decade has documented high and increasing HCC incidence resulting from chronic HBV and HCV infections. It is clearly shown that HB vaccination is implemented in the national immunization programmes and that immunization is highly effective in the preventing chronic HBV infection. In the absence of vaccination for HCV, further investigation of the risk factors and modes of transmission of HCV is required to reduce infection rates and to prevent future cases of HCC **(Anwar *et al.*, 2008)**.

The portal vein forms at the junction of the splenic vein and the superior mesenteric vein behind the pancreatic head, and it can become thrombosed or obstructed at any point along its course. In cirrhosis and hepatic malignancies, the thromboses usually begin intrahepatically and spread to the extrahepatic portal vein. In most other etiologies, the thromboses usually start at the site of origin of the portal vein.

Occasionally, thrombosis of the splenic vein propagates to the portal vein, most often resulting from an adjacent inflammatory process such as chronic pancreatitis. Inherited and acquired disorders of the coagulation pathway are frequent causes of portal vein thrombosis. Inherited disorders include mutations in the prothrombin gene G20210A as well as deficiencies of various intrinsic anticoagulation factors, such as protein C and protein S, and activated

protein C resistance. Acquired disorders include antithrombin III deficiency resulting from malnutrition, sepsis, disseminated intravascular coagulation, inflammatory bowel disease, liver disease, or estrogen use.

Acute portal vein thrombosis is a difficult clinical diagnosis because of the wide variety of clinical presentations. In up to 60% of cases, an underlying systemic prothrombotic disorder can be identified as an etiological factor. One third of cases are caused by local factors and the coexistence of several entities is not unusual **(Seijo-Ríos and García-Pagán, 2010).**

Des-gamma carboxyprothrombin (DCP), also known as protein induced by vitamin K absence/antagonist-II (PIVKA-II), is an abnormal form of the coagulation protein, prothrombin. Normally, the prothrombin precursor undergoes post-translational carboxylation (addition of a carboxylic acid group) by gamma-glutamyl carboxylase in the liver prior to secretion into plasma. DCP/PIVKA-II may be detected in people with deficiency of vitamin K (due to poor nutrition or malabsorption) and in those taking warfarin or other medication that inhibits the action of vitamin K **(Cui *et al.*, 2002)**.

Aim of the Work:

The aim of our study was to evaluate the value of PIVKA-II measurement as an early predictor of portal vein obstruction among other factors when HCC on liver cirrhosis is diagnosed with trans-abdominal ultrasound. Early detection would facilitate clear plan of management at an early stage leading to better prognosis of patients.

2. Patients and Methods:

The present study included fifty newly diagnosed patients (37 males and 13 females) with proved histopathological diagnosis of HCC that were admitted to Hepatology Unit at Ain Shams University hospital. The study was conducted in the period from January 2009 –October 2011 . Patient's ages ranged from 35 to 63 years.

According to clinical, radiological and laboratory data patients with the following findings were excluded from the study: (1) patients on warfarin therapy; (2) patients receiving chemotherapy, radiotherapy or local injection for the tumor; (3) patients with multiple organ failure including hepato-renal syndrome (HRS); (4) patients with extra hepatic malignancies metastasizing the liver; and (5) patients with pancreatic and biliary diseases.

History Taking:

Careful history taking was taken from all included patients with stress on the symptoms of chronic liver disease as fever, jaundice, bleeding tendency, episodes of hematemesis and melena, right hypochondrial pain or palpable mass, ascites, and lower limb edema. Also, history of bilharziasis, antibilharzial treatment, in addition to drug intake history including supplementary vitamin K, warfarin and antibiotics were included in the history.

General Examination:

General examination with special stress on manifestations of liver cell failure as fever, jaundice, bleeding tendency, edema of lower limbs, flappy tremors, spider naevi and fetor hepaticus. Examination for lymph node enlargement was also done.

Local Examination:

Examination for liver masses. Examination of size of spleen and presence of ascites with exclusion of other abdominal masses.

Radiological Examination:

Abdominal ultrasonographic examination and dynamic computed tomography scanning were done in fasting state evaluating:

- The liver for size, echo pattern and presence or absence of focal lesions (detected masses were evaluated as regards site, echo pattern, size).
- The spleen for size
- Portal vein diameter (normally regarded as 9-12 mm) and presence or absence of thrombosis.
- Presence or absence of hepatic periportal fibrosis.
- Abdominal lymph node enlargement (para aortic & porta hepatis).
- Presence of ascites.

Laboratory Investigations:

- Complete blood picture (CBC)
- Erythrocyte sedimentation rate (ESR).
- Prothrombin time (PT) and international normalized ratio (INR).
- Liver function tests (ALT, AST, ALP, serum albumin and serum bilirubin) :
- Kidney function tests (serum creatinine).
- Alpha feto protein (AFP) determination (using AFP Mab ELISA Kit by EQUIPAK).expressed as ng/ml
- Serum PIVKA-II level determination using micro cup type enzyme immunoassay test kit (Eitest PIVKA-II kit by sanko junyako – Tokyo Japan): **(Amiral *et al.*, 1990)** results expressed as mAU/ml(micro arbitrary units)

Statistical methods

- Statistical analysis of the data was performed by using SPSS 15 software package under Windows 7® operating system. Categorical data parameters were presented in the form of frequency and percent. All categorical data comparisons and associations were analyzed by either chi square test or Fisher exact test according to the nature of

data. Continuous data parameters were described as mean, SD (standard deviation), median and IQR (interquartile range). Analysis for normality of data was performed by using Shapiro Wilk test and Kolmogorov Smirnov test. Normally distributed variables were analyzed for difference between independent samples by using Student' t-test and correlated by using Pearson's correlation matrix. Non-parametric variables were analyzed for difference between independent samples by using Mann Whitney U test and correlated by using Spearman correlation test. Receiver Operating Characteristics (ROC) curve was plotted for determination of the cut-off point at which the relevant studied variable achieves best diagnostic performance. Probability level (*P* value) was assumed significant if less than 0.05 and highly significant if P value was less than 0.001. *P* value was considered non-significant if greater than or equal to 0.05. Graphic presentation of data was done by using EXCEL ® 2010 software.

3. Results:

The present study was conducted on fifty patients with HCC who attended Ain Shams University Hospital from January 2009 to October 2011. Patients were classified into two groups after diagnosis of portal vein thrombosis. The study included 37 males within which 18 were diagnosed as having PVT (48.6%) and 13 females, with only 4 cases diagnosed with PVT (30.8%) with non-significant difference between both gender groups. Forty three patients (86.0%) were positive for HCV when screened with Hepatits C Ab by ELISA and two patients were positive for HBsAg (4.0%). The remaining 5 patients did not prove positive on screening with viral markers (Table 1). Moreover, all studied laboratory parameters did not prove any significance in comparing both patients with PVT versus those without PVT (Table 2).

Diagnostic performance of PIVKA-II was tested at different cut-off points and was expressed in terms of sesnitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy. Thirty seven patients, out of the studied 50 cases, were correctly classified as having PVT at cut-off value >100mAu/ml (Table 3).

Table (1): Comparison between both studied groups as regards age, sex and hepatitis viruses

Parameters		No PVT (n=29)			PVT (n=21)			t/X^2	*p*	SIg
Age years	X±SD	52.97	±	8.74	54.76	±	4.56	0.943t	0.351	NS
	Range	35	-	63	44	-	63			
Sex	M	19 (51.4%)			18 (41.6%)			0.910	0.340	NS
	F	9 (69.2%)			4 (30.8%)					
HCV	-ve	5 (71.4%)			2 (28.6%)			0.603	0.684f	NS
	+ve	24 (55.8%)			19 (44.2%)					
HBV	-ve	27 (56.3%)			21 (43.8%)			1.509	0.503f	NS
	+ve	2 (100%)			0 (0%)					

Table (2): Comparison between both studied groups as regards PIVKA-II and AFP

Parameters		No PVT (n=29)			PVT (n=21)			z	*p*	SIg
PIVKAII mAu/ml	X±SD	40.2	±	40.6	97.0	±	81.3	2.575	0.010	S
	Median	39.2			88.4					
	Range	0.2	-	146.3	0.8	-	266.3			
AFP ng/ml	X±SD	628.2	±	1827.6	831.8	±	1865.7	1.632	0.103	NS
	Median	114.0			146.0					
	Range	1.0	-	9453.0	6.0	-	8457.0			

In the present study, a statistically higher PIVKA-II (z=2.575; *p*=0.010) has been found in patients with PVT on comparison with patients without PVT. PIVKA-II levels were 97.0mAu/ml±81.3 (median=88.4), with a range from 0.8 to 266.3 for patients with PVT and 40.2mAu/ml±40.6 (median=39.2), with a range from 0.2 to 146.3 for patients without PVT (Table 3, Figure 1).

On the other hand, AFP showed statistically non-significant difference between both studied groups. AFP levels were 831.8ng/ml±1865.7 (median=146.0), with a range from 6.0 to 8457.0 for patients with PVT and 628.2ng/ml±1827.6 (median=114.0), with a range from 1.0 to 9453.0 for patients without PVT (Table 2, Figure 1).

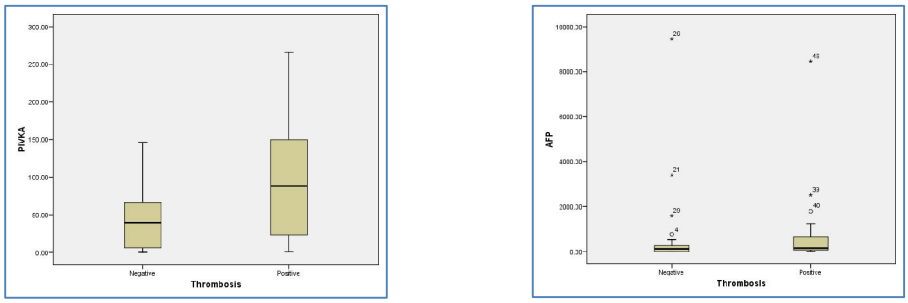

Figure 1: Box plot demonstrating the median, Inter-quartile range and outliers of both PIVKA-II and AFP in both PVT and non-PVT patients groups

Table (3): Diagnostic performance of PIVKA-II

		PIVKA-II >40mAu/ml		PIVKA-II >100mAu/ml		PIVKA-II >200mAu/ml	
		<40	>40	<100	>100	<200	>200
Thrombosis	- ve (n=29)	15	14	27	2	29	0
	+ ve (n=21)	8	13	11	10	18	3
Association between thrombosis and PIVKA-II	X^2	0.911		11.074		4.407	
	P	0.340		0.001		0.068	
	Sig	NS		HS		NS	
Diagnostic Performance of PIVKA-II at different cut-off points	TP	13		10		3	
	TN	15		27		29	
	FP	14		2		0	
	FN	8		11		18	
	Sens	61.9%		47.6%		14.3%	
	Spec	51.7%		93.1%		100.0%	
	PPV	48.1%		83.3%		100.0%	
	NPV	65.2%		71.1%		61.7%	
	DA	56.0%		74.0%		64.0%	

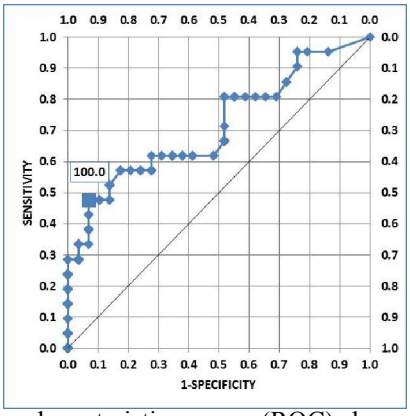

Figure 2: Receiver operating characteristics curve (ROC) demonstrating the relation between sensitivity and 1-specificity of PIVKA-II at different cut-off points.

Logistic regression analysis revealed that the PIVKA-II was the best sigle regressor parameter among others for prediction of PVT (x2=9.630, *p*=0.002). Addition of tumor number to PIVKA-II showed improvement in the predictive value of the model (x2=10.170, *p*=0.001) (Table 4).

Table (4): Stepwise binary logistic regression for demonstration of the best predictive model of PVT

	B coefficient	SE	Wald X^2	Sig	Exp(B)	95% CI	
						Lower	Upper
Single regressor model (omnibus x^2=9.630, p=0.002)							
PIVKA-II	0.015	0.006	7.244	0.007	1.015	1.004	1.027
Constant	-1.305	0.469	7.740	0.005	0.271		
Double regressor model (omnibus x^2=10.170, p=0.001)							
Number of lesions	1.873	0.657	8.125	0.004	6.506	1.795	23.583
PIVKA-II	0.019	0.007	7.637	0.006	1.019	1.005	1.033
Constant	-4.260	1.221	12.164	0.000	0.014		

4. Discussion:

With intrahepatic processes such as cirrhosis and tumor, thrombosis begins within the liver and spreads to the extrahepatic portal vein. In the majority of other etiologies, thrombosis begins at the origin of the portal vein. It is also possible for thrombosis of the splenic vein to propagate to the portal vein. This may occur when there is an adjacent inflammatory process such as chronic pancreatitis **(Gomez *et al.*, 2003)**.

In liver cirrhosis there are many factors which create favorable circumstances for portal thrombosis: decreased portal flow and low levels of protein C, S and antithrombin III due to diminished synthesis. However, the studies published by now sustain that there are no differences between the levels of anticoagulant proteins (plasminogen, protein C, protein S or antithrombin III) among cirrhotic patients with or without PVT **(Hadzic, 2004)**.

Once HCC appears, PVT is noticed with higher incidence, up to 35% **(Webster *et al.*, 2005)**. Other studies point out that incidence of PVT in hepatocellular carcinoma varies about 20-30% in small HCC (< 3cm), up to 50-75% in HCC > 5 cm **(Jiang *et al.*, 2004)**.

The thrombotic factors produced by the tumor, the vascular compression or invasion, are proposed mechanisms (**Pasiri and Pirathvisuth, 2000)**. Although, PVT significantly modifies the prognosis of HCC patients **(Minagawa *et al.*, 2001)**, some studies in the literature state that PVT does not influence the survival of HCC patients **(Pasiri *et al.*, 1998**).

No relation has been found between gender and development of PVT. In the present study out of 37 males included, 18 patients had PVT in comparison to female gender which showed 4 patients with PVT out of 13 included in the study. Although the association was statistically non-significant, however male gender showed slightly higher frequency of PVT (48.6%) in comparison to females (30.8%) within patients with HCC. Similar finding has been identified by **Chawla and Dhiman (2008)** who found a slight male predominance in patients whose obstruction is secondary to liver cirrhosis.

The distribution of the age of presentation of portal vein thrombosis reflects the demographics of the underlying disease process. Primary portal vein thrombosis from coagulopathies occurs with equal frequency in adults and children. The frequency of portal vein obstruction from tumor compression or invasion is greater in adults **(Abd El-Hamid *et al.*, 2008)**. The current study did not reflect the impact of age on the PVT as all patients included were among the older age group. All patients included had an average age of 53.7±7.3 years. However, patients with PVT were slightly older than those without PVT. Mean age was 54.76±4.56 in PVT group and 52.97±8.74 in patients without PVT.

In agreement, non-specific upper right quadrant pain has been the main complaint in 19 out of 50 patients included in the current study. Those patients were equally distributed among both groups. Although, the difference between both groups was statistically non-significant, a higher incidence of upper right quadrant pain was detected in patients with PVT. Nine out of 21 patients with PVT (42.9%) suffered from upper right quadrant pain, while 9 out of 29 patients without PVT (31.0%) had suffered from the same complaint.

Also, fever was the chief complaint in 4 PVT patients (19.0%) and 3 patients without PVT (10.3%), with non-significant difference between both groups. Moreover, hematemesis was the presenting symptom in 6 PVT patients (28.6%) and 8 patients without PVT (27.6%)

Patel *et al.* (2001) found that in patients with PVT, when there are symptoms, they are primarily right upper quadrant pain and/or fever. Other presentations include increasing ascites, intestinal ischemia and its associated symptoms, and worsening symptoms of portal hypertension. There are also cases of acute esophageal bleeding **(Patel *et al.*, 2001)**.

Following an acute episode, there are certainly cases of complete and partial resolution. This adds to the belief that a significant number of acute episodes go unnoticed. Those patients who have chronic PVT usually have symptoms related to portal hypertension. In 90% of cases, the presenting complaint is an esophageal bleed. Chronologically, this may occur as long as 4 years later and there have been reports of a delay as long as 12 years **(Radovich, 2000)**.

If malignancy is the etiology of PVT, there is a lower incidence of bleeding. The harsh reality is that they do not survive long enough to develop the sequelae of portal hypertension. On rare occasions, patients with PVT will present with a fever of unknown origin **(Sheen *et al.*, 2000)**.

On physical examination, more than three quarters of patients have splenomegaly. Ascites is uncommon. Most symptoms are contingent upon the degree of underlying liver disease. A unique physical finding is the so called caput medusae. This nest of dilated veins forms because following posthepatic or intrahepatic hypertension, there is recanalization of the umbilical vein. This vein connects with the left hepatic branch of the portal vein, and its recanalization will not be observed in isolated extrahepatic portal vein obstruction because the obstruction is below the origin of the umbilical vein **(Amitrano *et al.*, 2009)**.

In PVT patients, liver function is typically conserved. Laboratory investigations will be normal or quite normal, unless there is coexistence of a liver disease. However, levels of prothrombin and other coagulation factors could be moderately decreased, while D-dimer is usually increased **(Condat and Valla, 2006).**

PVT is considered a milestone in the natural history of liver cirrhosis and it is related to serious complications, morbidity, and mortality, as previously discussed**.** Thus, prevention is the first aim of PVT management in patients with an advanced liver disease **(Garcia-Pagan and Valla, 2009)**.

Portal vein obstruction does not affect liver function unless the patient has an underlying liver disease such as cirrhosis. This is partially due to a rapid arterial buffer response, with compensatory increased flow of the hepatic artery maintaining the total hepatic blood flow. Formation of collaterals occurs rather rapidly as well, and they have been described as early as 12 days after acute thrombosis, though the average time to formation is approximately 5 weeks **(Chawla and Dhiman, 2008)**.

Recently, several studies tried to identify the strongest predictive factors for PVT development in these patients. In the past; male sex, previous surgery or interventional treatment for portal hypertension, previous variceal bleeding, low platelet count, and advanced liver failure have been associated with an increased risk of PVT development **(Francoz *et al.*, 2005).**

None of the liver function tests that were included in the current study revealed significance in differentiating patients with PVT. The present study showed that ALT and AST liver enzymes, PT and its INR, PTT, total bilirubin and serum albumin had a non-significant difference between patients with PVT in comparison to patients that didn't develop PVT.

In the present study, there was non-significant association between PVT on one side and both HCV and HBV on the other side. Similarly, **Koike *et al.* (2001)** in their study found that twenty-three patients were positive for HBsAg, 184 patients were positive for HCV Ab, 4 patients were positive for both, and 16 patients were negative for both. They found non-significant association between the presence of hepatitis viruses and incidence of portal vein occlusion after 1- and 2-year duration.

The rise of PIVKA-II levels in HCC with PVT could be explained by the fact that, the invasive activities of HCC towards the extra hepatic direction are reflected in its extra hepatic venous invasion at the portal vein including tumor emboli, have a positive relationship with PIVKA-II levels **(Suehiro, 1995).** Moreover, **Volk *et al.* (2007)** also reported that there is a possibility that the growth factor like action of PIVKA-II increases the invasive behavior of HCC. Many reports state high PIVKA-II levels to be of poor prognostic value. It has been shown that patients with high PIVKA-II and high AFP levels show poor prognostic factors **(Utsunomiya *et al.*, 2001; Maeda *et al.*, 2002; Kaibori *et al.*, 2004; Soejima *et al.*, 2007).**

The current study tried to link the PIVKA-II level with the development of PVT as one of the poor prognostic factors during the disease progression in HCC patients. Accordingly, a significantly higher PIVKA-II (p=0.010) has been found in patients with PVT 97.0mAu/ml±81.3 (median=88.4) on comparison with patients without PVT 40.2mAu/ml±40.6 (median=39.2). Binary forward logistic regression analysis has been used for determination of the most significant predictors among others of PVT. Study revelaed that the most significant "single regressor" model was that model that included PIVKA-II. The best model was that included both PIVKA-II and number of tumor masses.

For determination of the best PIVKA-II cut-off value that best predicts PVT, a receiver operating characteristics curve (ROC curve) has been plotted. The best cut-off value of PIVKA-II that best predicts the PVT was 100 mAU/mL. AT this cut-off point the diagnostic performance of PIVKA-II was 74.0% with 47.6% sensitivity and 93.1% specificity with a highly significant association between the studied marker and PVT.

Similarly, **Koike *et al.* (2001)** on their study stated that stepwise multivariate Cox regression analysis demonstrated that PIVKA-II levels at the time of initial diagnosis of HCC was the most significant predisposing factor for the development of PVI followed by the histologic tumor grade. In fact, of the 24 patients who developed PVI during follow-up, serum PIVKA-II levels increased in 23 patients before PVI was detected, whereas AFP levels remained below 100 ng/mL in 7 patients, even after the appearance of PVI (data not shown). Serum PIVKA-II levels increased 7 months (range, 1–22 months) before PVI development.

Okuda *et al.* (2001) reported that PIVKA-II has been regarded as being closely related to a higher incidence of portal vein invasion, intrahepatic metastasis, and worse prognosis. Moreover, a recent study done by **Masuzaki *et al.* (2008)** also revealed that higher PIVKA-II is associated with increased risk of portal vein invasion of HCC. These results are also similar to that found by **Kimura *et al.* (2008).**

There are several studies that have examined the parameters that contribute to PVI: Tumor size, declines in the histologic grading of tumor cell

differentiation, and the presence of a fibrous capsule around tumor have been shown to be indicators of later development of PVI **(Adachi *et al.,* 1996)**. According to the plenty of studies that link between PIVKA-II and prognosis in HCC, a prognostic staging system in which PIVKA-II has been incorporated is being suggested. From an analysis of 141 patients **Kawakita *et al.* (2003)** concluded PIVKA-II ≥ 100 mAU/mL to be a prognostic factor, and the authors suggested a stage classification in which PIVKA-II ≥100 mAU/mL should be incorporated into the CLIP score. **Nanashima *et al.* (2003)** concluded that PIVKA-II ≥400 mAU/mL was a poor prognostic factor and suggested modified CLIP scoring. Moreover, **Omagari *et al.* (2004)** suggested the SLiDe score combined with stages and liver damage, and **Toyoda *et al.* (2006)** suggested the BALAD score that can predict the prognosis only by measuring bilirubin, albumin, AFP-L3, AFP, and PIVKA-II using preoperative serum samples, according to an analysis of 2600 patients.

As regards AFP, there was non-significant difference between both studied groups. AFP levels were 831.8±1865.7 (median=146.0) in patients with PVT and 628.2±1827.6 (median=114.0) in patients without PVT.

Suehiro *et al.*(1994) found that PIVKA-II has a lower sensitivity, but higher specificity than AFP, and the use of these two complementary markers appears to be useful in the diagnosis of HCC. The frequencies of intrahepatic metastasis, portal vein tumor thrombus, hepatic vein tumor thrombus, and capsular infiltration were significantly higher in patients with positive PIVKA-II than in those with negative-PIVKA-II, and the recurrence-free rate was significantly lower in patients with positive rather than with negative PIVKA-II. However, there were no significant differences between the patients who were AFP positive and those who were AFP negative in pathologic prognostic factors and the recurrence-free rate. The authors concluded that PIVKA-II may be a useful marker for the prediction of intrahepatic spread and for the prognosis of HCC. In addition, PIVKA-II-positive patients, thus, need aggressive postoperative adjuvant therapy for undetectable residual tumors and careful postoperative monitoring to enable the early recognition of recurrence.

Other reports have indicated that PVI is observed more frequently in patients with positive serum PIVKA-II levels compared with patients who have negative serum PIVKA-II levels **(Liebman *et al.,* 1984Sakon et al., *et al.,* 1992;)**. In those previous studies, these parameters were selected retrospectively using cross-sectional analysis.

In conclusion serum PIVKA II levels >100mAu/ml is a predictor for development of PVT in patients with HCC and which influences the therapeutic options available for the patients

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References:

1. **Abd El-Hamid N, Taylor RM, Marinello D, Mufti GJ, Patel R and Mieli-Vergani G (2008):** Aetiology and management of extrahepatic portal vein obstruction in children: King's College Hospital experience. J Pediatr Gastroenterol Nutr.; 47(5):630-4.
2. **Adachi E, Maeda T, Kajiyama K and Tsuneyosi M (1996):** Factors correlated with portal venous invasion by hepatocellular carcinoma. Univariate and multivariate analyses of 232 resected cases without preoperative treatments. Cancer; 77:2022–31.
3. **Amiral J, Grosley M and Plassart V (1990):** A new monoclonal based test for the assay of Decarboxy-prothrombin (DCP) in hepatocarcinomas. GEHTde Mahouse; 19-20 october: page 1.
4. **Amitrano L, Guardascione MA, Menchise A, Martino R, Scaglione M and Giovine S (2009):** Safety and Efficacy of Anticoagulation Therapy With Low Molecular Weight Heparin for Portal Vein Thrombosis in Patients With Liver Cirrhosis. J Clin Gastroenterol.44(6))448-451.
5. **Anwar WA, Khaled HM, Amra HA, El-Nezami H, Loffredo CA (2008):** Changing pattern of hepatocellular carcinoma (HCC) and its risk factors in Egypt: Possibilities for prevention. Mutat Res; 659(1-2):176-84.
6. **Bruix J and Sherman M (2005):** Management of hepatocellular carcinoma. Hepatology; 42:1208–36.
7. **Chawla Y and Dhiman RK (2008):** Intrahepatic portal venopathy and related disorders of the liver. Semin Liver Dis.; 28(3):270-81.
8. **Condat B and Valla D (2006):** Nonmalignant portal vein thrombosis in adults. Nat Clin Pract Gastroenterol Hepatol; 3:505–515.
9. **Cui R, Wang B, Ding H, Shen H, Li Y and Chen X (2002):** Usefulness of determining a protein induced by vitamin K absence in detection of hepatocellular carcinoma. Chin Med J; 115: 42–5.
10. **Everhart JE (2008):** Primary Liver Cancer. In: Everhart JE, editor. Burden of Digestive Diseases in the United States. US Government Printing Office; Washington, DC: 2008. pp. 49–52.

11. **Francoz C, Belghiti J, Vilgrain V, Sommacale D, Paradis V, Condat B, Denninger MH, Sauvanet A, Valla D, Durand F (2005):** Splanchnic vein thrombosis in candidates for liver transplantation: usefulness of screening and anticoagulation. Gut. 2005;54:691-697.
12. **Garcia-Pagan JC and Valla DC (2009):** Portal vein thrombosis: a predictable milestone in cirrhosis. J Hepatol; 51:632–634.
13. **Gomez M, Garcia ES, Lopez-Lacomba D (2003):** Antiphospolipides antibodies are related to portal vein thrombosis in cirrhotic patients. J Clin Gastroenterol; 31:237-240
14. **Hadzic N (2004):** Hepatic veno-occlusive disease and portal vein thrombosis; closer than we think. Eur J of Cancer; 40:2643-2644.
15. **Jiang ZB, Shang H and Shen XY (2004):** TIPS for palliative treatment of portal hypertension secondary to portal vein tumor thrombosis. World J Gastroenterol; 10:1881-1884.
16. **Kaibori M, Matsui Y, Yanagida H, Yokoigawa N, Kwon AH and Kamiyama Y (2004):** Positive status of alpha-fetoprotein and desgamma-carboxy prothrombin: important prognostic factor for recurrent hepatocellular carcinoma. World J Surg.; 28: 702-707.
17. **Kamangar F, Dores GM and Anderson WF (2006):** Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. J Clin Oncol.;24:2137–50.
18. **Kawakita T, Shiraki K, Yamanaka Y, Yamaguchi Y, Saitou Y, Enokimura N, Yamamoto N, Okano H, Sugimoto K, Murata K, Yamakado K, Takeda K and Nakano T (2003):** A new prognostic scoring system involving des-gamma-carboxy prothrombin as a useful marker for predicting prognosis in patients with hepatocellular carcinoma. Int J Oncol; 23: 1115-1120.
19. **Kimura N, Hakamada K, Miura T, *et al.* (2008):** Des-gamma-carboxy prothrombin as an important prognostic indicator in patients with small hepatocellular carcinoma. World J Gastroenterol; 14(9): 1370-1377.
20. **Koike Y, Shiratori Y, Sato S, Obi S, Teratani T, Imamura M, Yoshida H, Shiina S, Omata M (2001):** Des-gamma-carboxy prothrombin as a useful predisposing factor for the development of portal venous invasion in patients with hepatocellular carcinoma: a prospective analysis of 227 patients. Cancer; 91:561-569.
21. **Liebman HA, Furie BC, Tong M, Blanchard RA, Lo KJ and Lee SD (1984):** Des-g-carboxy (abnormal) prothrombin as a serum marker of primary hepatocellular carcinoma. N Engl J Med; 310:1427–31.
22. **Maeda S, Fujiyama S, Tanaka M, Ashihara H, Hirata R and Tomita K (2002):** Survival and local recurrence rates of hepatocellular carcinoma patients treated by transarterial chemolipiodolization with and without embolization. Hepatol Res; 23: 202-210.
23. **Masuzaki R, Yoshida H, Tateishi R, (2008):** Hepatocellular carcinoma in viral hepatitis: Improving standard therapy. Best Practice and Research Clinical Gastroenterology; 22 (6); 1137–1151.
24. **Malkowski P, Pawlak J, Michalowicz B, *et al.* (2003):** Thrombolytic treatment of portal thrombosis. Hepatogastroenterology; 50: 2098-2100.
25. **Minagawa M, Makuuchi M and Takayama T (2001):** Selection criteria for hepatectomy in patients with hepatocellular carcinoma and portal vein tumor thrombus. Ann Surg; 233:379-384.
26. **Nanashima A, Morino S, Yamaguchi H, Tanaka K, Shibasaki S, Tsuji T, Hidaka S, Sawai T, Yasutake T and Nakagoe T (2003):** Modified CLIP using PIVKA-II for evaluating prognosis after hepatectomy for hepatocellular carcinoma. Eur J Surg Oncol; 29: 735-742.
27. **Northup PG, Sundaram V, Fallon MB, *et al.*(2008):** Hypercoagulation and thrombophilia in liver disease. J Thromb Haemost; 6: 2-9.
28. **Okuda H, Nakanishi T, Takatsu K, *et al.* (2001):** Comparison of clinicopathological features of patients with hepatocellular carcinoma seropositive for a-fetoprotein alone and those seropositive for des-g-carboxy prothrombin alone. Journal of Gastroenterology and Hepatology; 16, 1290–1296.
29. **Omagari K, Honda S, Kadokawa Y, Isomoto H, Takeshima F, Hayashida K, Mizuta Y, Murata I and Kohno S (2004):** Preliminary analysis of a newly proposed prognostic scoring system (SLiDe score) for hepatocellular carcinoma. J Gastroenterol Hepatol; 19: 805-811
30. **Parisi M, Avellini C and Fabris C (1998):** Portal vein thrombosis in hepatocellular carcinoma: age and sex distribution in an autopsy study. J Cancer Res Clin Oncol; 124:397- 400
31. **Pasiri S and Pirathvisuth T (2000):** Review of 336 patients with hepatocellular carcinoma. World J Gastroenterol; 6:339-343.
32. **Patel N, Haskal ZJ and Kerlan RK (2001):** Portal Hypertension: Diagnosis and Interventions. 2nd ed. Society of Cardiovascular and Interventional Radiology.
33. **Radovich PA (2000):** Portal vein thrombosis and liver disease. J Vasc Nur; 18(1):1-5.

34. **Sakon M, Monden M and Wakasa K (1992):** Relationship between pathologic prognostic factors and abnormal levels of des-gcarboxy prothrombin and a-fetoprotein in hepatocellular carcinoma. Am J Surg; 6:251–6.
35. **Seijo-Ríos S and García-Pagán JC (2010):** Portal vein thrombosis].Gastroenterol Hepatol. 2010 Mar;33(3):179-90. Epub 2009 Sep 5.
36. **Sheen CL, Lamparelli H and Milne A (2000):** Clinical features, diagnosis and outcome of acute portal vein thrombosis. QJM; 93(8):531-4.
37. **Soejima Y, Taketomi A, Yoshizumi T, Uchiyama H, Aishima S, Terashi T, Shimada M and Maehara Y (2007):** Extended indication for living donor liver transplantation in patients with hepatocellular carcinoma. Transplantation; 83: 893-899
38. **Stravitz RT, Heuman DM, Chand N, Sterling RK, Shiffman ML, Luketic VA, Sanyal AJ, Habib A, Mihas AA, Giles HC, Maluf DG, Cotterell AH, Posner MP and Fisher RA (2008):** Surveillance for hepatocellular carcinoma in patients with cirrhosis improves outcome. Am J Med; 121:119–26.
39. **Suehiro T, Sugimachi K, Matsumata T, Itasaka H, Taketomi A and Maeda T (1994):** Protein induced by vitamin K absence or antagonist II as a prognostic marker in hepatocellular carcinoma. Cancer; 73:2464–71.
40. **Suehiro T, Matsumata T, Itasaka H, Taketomi A, Yamamoto K and Sugimachi K (1995):** Des-gamma carboxy prothrombin and proliferative activity of hepatocellular Carcinoma. Surgery; 177:682-91.
41. **Toyoda H, Kumada T, Osaki Y, Oka H, Urano F, Kudo M and Matsunaga T (2006):** Staging hepatocellular carcinoma by a novel scoring system (BALAD score) based on serum markers. Clin Gastroenterol Hepatol; 4: 1528-1536.
42. **Utsunomiya T, Shimada M, Shirabe K, Kajiyama K, Gion T, Takenaka K and Sugimachi K (2001):** Clinicopathological characteristics of patients with extrahepatic recurrence following a hepatectomy for hepatocellular carcinoma. Hepatogastroenterology; 48: 1088-1093.
43. **Volk ML, Hernandez JC, Su GL, Lok AS and Marrero JA (2007):** Risk factors for hepatocellular carcinoma may impair the performance of biomarkers: a comparison of AFP, DCP, and AFP-L3.Cancer Biomark; 3(2):79-87.
44. **Webster GJM, Burroughs AK and Riordan SM (2005):** Review article: portal vein thrombosis: new insights into aetiology and management. Aliment Pharmacol Ther; 21(1):1-9.

10/5/2012