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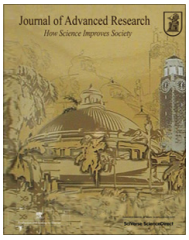

ORIGINAL ARTICLE

Impact of PIVKA-II in diagnosis of hepatocellular carcinoma

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KEYWORDS

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Abstract Liver cancer grows silently with mild or no symptoms until advanced. In the absence of an effective treatment for advanced stage of hepatic cancer hope lies in early detection, and screening for high-risk population. Among Egyptians viral hepatitis is the most common risk factor for hepatocellular carcinoma (HCC). The current work was designed to determine the level of prothrombin induced by vitamin K absence-II (PIVKA-II) in sera of patients suffering from HCC and hepatitis C virus (HCV) patients being the most common predisposing factor for HCC. Our ultimate goal is diagnosis of HCC at its early stage. The current study was carried out on 83 individuals within three groups; Normal control, HCV and HCC groups. Patients were subdivided into cirrhotic and non-cirrhotic. Complete clinicopathological examination was carried out for each individual to confirm diagnosis. Individuals' sera were subjected to quantitative determination of alpha-fetoprotein (AFP), PIVKA-II and other parameters. PIVKA-II proved to be superior to AFP for early detection of HCC patients being highly sensitive and specific. Furthermore it has the ability to discriminate between different histopathological grades of HCC and It has a powerful diagnostic validity to evaluate the thrombosis of portal vein and to differentiate between early and late stages of HCC. The direct relation between the level of PIVKA-II and the size of tumor makes it an attractive tool for early HCC diagnosis and surveillance. Using the best cut-off value of AFP (>28), showed a sensitivity of (44%) and specificity of (73.3%). While cut-off value of PIVKA-II (>53.7) showed 100% sensitivity and specificity.

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Introduction

Hepatocellular carcinoma (HCC) is an important cause of death worldwide [1,2]. It is the sixth most common cancer worldwide and the third cause of cancer death [3]. It kills more than 650,000 people around the world annually [4]. Incidence

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of HCC has risen over the last 5–8 years with no significant change in the survival rate in the last two decades [5].

In Egypt, Liver malignancies constitute 11.75% of the malignancies of the digestive organs and 1.6% of total malignancies. HCC ranks number one with an incidence rate of 70.48% [6].

The etiology of HCC differs according to geographic, economic, and health status. The most common causes are alcohol consumption [7], hepatitis C and B viruses [8] and chronic necro-inflammatory hepatic disease. Commonly cirrhosis is present in 60–80% of patients with HCC [9]. Among Egyptian patients HCV and HBV infections are the most common risk factors for HCC. About 10% – 20% of the general Egyptian population is infected with HCV [10]. Approximately 90% of Egyptian HCV isolates belong to subtype (4a) which responds less successfully to interferon therapy than other subtypes [11]. Most of the HCC occurs in cirrhotic patients associated with viral infection. However, 10–25% of cases develop in absence of cirrhosis. This is due to the direct oncogenic effect of HBV as HBV-DNA genome integrates in hepatocellular chromosomes [12]. In contrast HCV exerts its carcinogenic effect probably through production of cirrhosis [13]. Many studies showed that HCV has a direct oncogenic action through its core component [14].

All these facts made it essential to find sensitive markers for early diagnosis and monitoring of recurrence of HCC [15].

Ultrasound examination of the liver and detection of AFP level in serum are commonly used to screen for liver cancer [16]. Although detection of AFP level is easy and less expensive, but it shows less sensitivity [17], since elevation in AFP level is common in patients with chronic liver disease, pregnancy and germ cell tumors. AFP titers also rise with flares of active hepatitis, and may be persistently elevated in patients with cirrhosis [18]. Ultrasound is better, but is more expensive, operator dependent and less reliable in the presence of cirrhosis [19]. Thus, new markers with high sensitivity and specificity are required.

Prothrombin induced by vitamin K absence-II (PIVKA-II) is also known as Des-gamma carboxyprothrombin (DCP) is an abnormal prothrombin protein that is increased in the sera of patients with HCC. Generation of (PIVKA-II) is thought to be a result of an acquired defect in the post-translational carboxylation of the prothrombin precursor in malignant cells [20]. The validity of PIVKA-II as a tumor marker for HCC patients has been reported by many investigators [21–23]. None of the known markers are optimal, however when used together their sensitivity increases [24,25].

The present study was designed to investigate the potential role of PIVKA-II as a diagnostic, non-invasive marker for HCC at its early stages and to assess its sensitivity and specificity as compared with the usual recommended marker AFP.

Patients and methods

This study was conducted on 72 patients and 11 apparently healthy individuals as control. Patients were initially subjected to complete clinical examination and abdominal ultrasonography. Blood samples were collected for complete blood picture, liver and kidney function tests, Fasting blood sugar, serum potassium and sodium levels using the standard laboratory methods [26]. Hepatitis markers HBs Ag, HBs Ab, HBc Ag and HCV Ab were detected using ELISA technique, HCV-RNA by qualitative PCR. Diagnosis of HCC was confirmed by triphasic CT scan or liver biopsy guided by U/S. Serum was collected and stored at −70 °C until assayed. Level of serum AFP was detected using ELISA technique (RADIM SpA, Italy) and PIVKA-II level in the plasma using ELISA kit (Stago Diagnostic, France).

Patients with cholangiocarcinoma, hepatoblastoma, hemangioma, or any other hepatic tumor rather than HCC and metastasizing to the liver were excluded from the study. The diagnosis was confirmed by abdominal ultrasound, triphasic CT scan of the abdomen and tissue biopsies for histopathological examinations. HCC's patients were classified according to Barcelona criteria [27], and patients with liver cirrhosis were classified according to Child- Pugh criteria [28].

The study was approved by the Ethical Committee of National Cancer Institute (NCI), Cairo University, which conforms to the code of ethics of the World Medical Association (Declarations of Helsinki). The study was explained to all individuals who were also informed with a written consent. Individuals were divided into three groups; group I (Control) consisted of 11 apparently healthy subjects, matched with patient's age and sex. Group II included patients who had history of HCV infection that was confirmed by laboratory findings. This group consisted of 24 patients, 17 of them were males and seven were females. Their median age was 51.5 years (33–70), half of them with cirrhosis. Group III Consisted of 48 patients with HCC who attended NCI clinic, Cairo University during the years 2007 to 2009. Thirty four were males and 14 females. Their median age was 59.5 years (38–77) (Table 1). A 52.1% of them were cirrhotic, 10 patients were Child A (20.8%), 33 Child B (68.8%) and five were Child C (10.4%). Patients were classified according to the Barcelona Clinic Liver Cancer" (BCLC) system into18 patients stage A (37.5%), seven patients stage B (14.6%), 18 patients stage C (37.5%) and five patients stage D (10.4%) Table 5. Patients were also classified according to their clinicpathological features including stage, grade and size of tumor.

Statistical analysis

Continuous variables were expressed as median (range) and were compared by using nonparametric (Mann–Whitney test) for two groups comparison and Kruskall–Wallis test for multiple group comparison. The ROC (receiver operator characterizing) curve was drawn, to improve the specificity and sensitivity of the studied parameters. The analysis was performed using SPSS, version 14.

Table 1 Demographic characteristics of the three groups of patients.

Parameter	Control	HCV	HCC
Sample size	11	24	48
Median age	34	51.5	59.5
Range	29–52	33–70	38–77
Sex			
Males *n* (%)	7 (63.63%)	17 (70.83%)	34 (70.8%)
Females *n* (%)	4 (36.36%)	7 (29.16%)	14 (29.25)

Values are expressed as medians (ranges) for age, and as number (percentage) for sex.