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Full Length Article

Comparing Prothrombin induced by vitamin K absence-II (PIVKA-II) with the oncofetal proteins Glypican-3, Alpha feto protein and Carcinoembryonic antigen in diagnosing hepatocellular carcinoma among Egyptian patients

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KEYWORDS

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Abstract *Background:* Hepatocellular carcinoma (HCC) is usually asymptomatic in the early stage and does not show elevated alpha-feto protein (AFP). AFP shows 60–80% sensitivity in diagnosing HCC.

Glypican3 (GPC-3) is an oncofetal protein that is only detected in HCC cells but not in benign liver tissues, while Carcinoembryonic antigen (CEA) is expressed in various neoplasms including HCC. Although, it is not specific for HCC.

Prothrombin induced by vitamin K absence-II (PIVKA-II) is an abnormal prothrombin protein that is increased in the serum of HCC patients. It has higher sensitivity and specificity compared to AFP. The aim of this study is to compare the clinical utility of PIVKA-II with GPC-3, AFP and CEA in diagnosing HCC.

Abbreviations: HCC, hepatocellular carcinoma; AFP, Alpha-feto protein; GPC-3, Glypican3; CEA, Carcinoembryonic antigen; PIVKA-II, Prothrombin induced by vitamin K absence-II

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Patients and methods: This study included 40 patients with HCC, 10 patients with cirrhosis as a benign control group, and 10 apparently healthy volunteers as normal controls.
Serum samples were subjected to routine laboratory investigations, measurement of CEA, AFP using MEIA technique (Axsym), glypican3, and PIVKA-II using ELISA technique in the sera of all patients and controls.
Results: All markers showed the highest results in the HCC group. Higher concentrations of PIVKA-II were detected in patients with splenomegaly, and in tumors with size (> 3 cm). Combination of Glypican-3 and PIVKA-II showed the highest sensitivity, while GPC-3 alone and combination of GPC-3 and AFP showed the highest specificity to differentiate HCC from liver cirrhosis and normal controls. GPC-3, PIVKAII, and combination of both showed the highest sensitivity, while GPC-3 alone showed the highest specificity to differentiate HCC from liver cirrhosis.
Conclusion: Glypican-3 is the only oncofetal antigen that showed comparable high diagnostic accuracy as PIVKA-II in diagnosing HCC among Egyptian patients.

Introduction

Hepatocellular carcinoma (HCC) is a major health problem [1]. It ranked 2nd most common cancer site among males and 7th among females in the National Cancer Institute (NCI), Cairo University, Egypt [2]. HCC is usually asymptomatic in the early stage and tends to be intravascularly and intrabiliary invasive. Moreover, early HCC does not show elevated alpha-feto protein (AFP) [3].

Oncofetal antigens are proteins produced during fetal life and disappear after birth. In cancer patients, these proteins reappear which demonstrates that certain genes are reactivated as the result of the malignant transformation of cells [4].

AFP is the only molecular marker widely used for the diagnosis of HCC. At a cutoff value of 20 ng/ml, serum AFP shows 60–80% sensitivity [5]. This sensitivity may decrease to about 40% for small tumors [6]. In addition, a significant increase in serum AFP level (20–200 ng/ml) is detected in a considerable number of patients with chronic liver disease [7].

Glypican3 (GPC-3) is an oncofetal protein member of the glypican family. It plays an important role in cell growth, differentiation and migration [8]. It is only detected in HCC cells but not in benign liver tissues [9]. Some studies investigated the role of GPC-3 as a marker for early stage of HCC [9–12]. They found it to be a sensitive and specific marker for the diagnosis of early HCC.

Carcinoembryonic antigen (CEA) is expressed in various neoplasms of endodermal origin including HCC. However, serum CEA levels alone are not specific for HCC [13].

Prothrombin induced by vitamin K absence-II (PIVKA-II) is an abnormal prothrombin protein that is increased in the serum of HCC patients as a result of an acquired defect in the posttranslational carboxylation of the prothrombin precursor in malignant cells [4]. Many studies showed that PIVKA-II has higher sensitivity and specificity compared to AFP in differentiating HCC from other chronic liver diseases [14–17].

The aim of this study is to compare the clinical utility of PIVKA-II with the oncofetal antigens; GPC-3, AFP and CEA in differentiating HCC patients from benign cirrhotic patients and normal controls, also to compare such markers with different prognostic factors of HCC.

Patients and methods

Patients

This study included 40 newly diagnosed HCC patients, all cases who were presented to the outpatients' clinic at the NCI, Cairo University, as well as the National Liver Institute, Cairo over a period of consecutive 9 months from January to September 2012, and were eligible for the study were included. Their age ranged from 44 to 77 years with a median of 59. They were proven to be HCC by computed tomography (CT) or magnetic resonance imaging (MRI).

Exclusion criteria: Prolonged obstructive jaundice, intrahepatic cholestasis with vitamin K deficiency and intake of warfarin or antibiotics.

The study also included 10 patients with cirrhosis as a benign control group who were diagnosed on the basis of clinical and radiological evidence. They were 8 males and 2 females. Their age ranged from 44 to 72 years with a median of 57. Also, 10 apparently healthy volunteers were included as normal controls; they were 5 males and 5 females, their age ranged from 36 to 44 years with a median of 40.

A written consent from all patients according to the international ethics committee guidelines, and IRB approval were obtained.

Blood samples from patients and controls were subjected to the following:

(1) Liver function tests using Beckman CX9 auto-analyser. Prothrombin time and concentration using Siemens turbitimer [18].
(2) Tumor Markers: AFP [19], CEA [20] were done using Axsym based on the microparticle enzyme immunoassay (MEIA) technology.
(3) PIVKA-II was done using BlueGene Biotech, Shanghai, China by ELISA technique.
(4) Glypican-3 was done using Uscn Life Science Inc. Wuhan, China by ELISA technique.

Haemolysed and lipemic samples were excluded.

Statistical analysis

Data were analyzed using IBM SPSS advanced statistics version 20 (SPSS Inc., Chicago, IL). For quantitative data,