Usefulness of determining a protein induced by vitamin K absence (PIVIKA-II) in diagnosis and prognosis of hepatocellular carcinoma.

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By

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فائدة تقرير البروتين الناتج عن نقص فيتامين ك (بيفكا ٢) فى تشخيص وتطور سرطان الخلايا الكبدية

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Summary

Hepatocellular carcinoma (HCC) is a major cause of morbidity and mortality: HCC is the seventh most common cancer worldwide, and the third leading cause of cancer-related deaths **(*Ferlay* et al., 2010).**

Hepatocellular carcinoma (HCC) is one of the commonest cancers worldwide. It is a major health problem and its incidence is increasing. The presence of cirrhosis of the liver is the major risk factor and worldwide this is largely due to chronic hepatitis C virus (HCV) and hepatitis B virus (HBV) infection. The diagnostic modalities, especially with respect to hepatic imaging, have improved in recent years. This, along with HCC surveillance in patients with cirrhosis, has led to the detection of HCC at an earlier stage, when curative therapy is likely to be more successful. The major diagnostic techniques for HCC include serum markers, various imaging modalities and histological analysis ***(Gomaa et al., 2009).***

Des-gamma-carboxyprothrombin (DCP) or prothrombin induced by vitamin K absence (PIVKA) is an abnormal prothrombin derived by an acquired defect in the post-translational carboxylation of the prothrombin precursor in HCC cells. DCP derived by reduction ccarboxylase activity that resulted in a lack of c-carboxylation of the glutamic-acid residues. The reduced activity of c-carboxylase was attributed to defective gene expression in HCC patients **(Grizzi et al., 2007).**

The aim of this work is to evaluate significance of serum level of PIVKA-II as a tumour marker for HCC and its importance in early detection of HCC.

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List of Abbreviations

A1AT	α1-antitrypsin
AASLD	American Association for the Study of LiverDisease
AFB1	Aflatoxin B1
AFP	Alpha fetoprotein
AFP-L3	Lens culinaris agglutinin-reactive
AFU	α -l-fucosidase
AIH	Autoimmune hepatitis
AJCC	American Joint Commission on Cancer
AKP	Alkaline phosphatase
ALT	Alanine aminotransferase
AP	Arterial phase
AST	Aspartate transaminase
BCLC	Barcelona Clinic Liver Cancer
BCS	Budd-Chiari syndrome
BFGF	Basic fibroblast growth factor (BFGF)
BMI	Body mass index
CBC	Complete blood count
CECT	Contrast-enhanced helical computed tomography
CEUS	Contrast enhanced ultrasound
CHC	Chronic hepatitis C
CLD	Chronic liver disease
CLIP	Cancer of the Liver Italian Program
cmm	Cubic millimeter
CT	Computed tomography

CUPI	Chinese University Prognostic Index
DCP	Des-gamma carboxyprothrombin
DL	Deciliter
DM	Diabetes Mellitus
DNs	Dysplastic nodules
DNA	Deoxyribonucleic acid
DP	Delayed phases
EASL	European Association for the Study of the Liver
ECM	Extracellular matrix
EFC	Epithelial- to-fibroblastoid conversion
ELISA	Enzyme Linked Immunosorbent Assay
EMT	Epithelial- to-mesenchymal transition
ESR	Erythrocyte Sedimentation Rate
EUS	Endoscopic ultrasound
FNAB	Fine needle aspiration biopsy
GGT	γ-glutamyl transferase
Gla	γ-carboxylated glutamic acid
Glu	glutamic acid
GP73	Golgi protein 73
GPC-3	Glypican-3
Hb	Haemoglobin
HBeAg	Hepatitis B e antigen
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B Virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HDL	High-density lipoprotein

HDV	Hepatitis D virus
HGDN	High-grade dysplastic nodules
HGF	Hepatocyte growth factor
HHC	Hereditary hemochromatosis
HLA	Human leukocyte antigen
HSCs	Hepatic stellate cells
HVD	Hepatic vena cava disease
HVOO	Hepatic venous outflow obstruction
IC	Immuno complexes
ICGHN	International Consensus Group for Hepatocellular Neoplasia
Ig	Immunoglobulin
IGF-II	Insulin-like growth factor-II
IL	Interleukin
INR	International normalized ratio
IVCO	Inferior vena cava
JIS	Japanese Integrated System
kD	Kilodalton
kgm	Kilogram
LCA	Lectin lens culinaris agglutin
LGDN	Low-grade dysplastic nodules
LR	Liver resection
LT	Liver transplantation
M	Meter
MAPK	Mitogen-activated protein kinase
MCP-1	Monocyte chemotaxis protein
MDCT	Multi-detector helical CT
Mg/dl	Milligram/deciliter

ML	Milliliter
MM	Millimeter
MOH	Ministry of Health
MPCT	Multi phasic helical computedtomography
MPD	Myeloproliferative disease
MRI	Magnetic Resonance Imaging
MUC-1	Mucin
MVA	Multivariate analysis
MVD	Micro vessel density
NAFLD	Non alcoholic fatty liver disease
NASH	Non alcoholic steatohepatitis
NCI	National Cancer Institutes
NCR	National Cancer Registry
OCs	Oral contraceptives
OS	Overall survival
PBC	Primary biliary cirrhosis
PDGF	Platelet derived growth factor
PEI	Percutaneous ethanol injection
PI3K	Phosphatidylinositol 3-kinases
PIVKA-II	Protien induced vit k abscence
PDGF	platelet-derived growth factor
PSC	primary sclerosing cholangitis
PT	Prothrombin time
PVC	Polyvinyl chloride
PVE	portal vein embolization
PVP	portal venous phase
PVT	Portal vein thrombosis

RBCs	Red blood cells
RFA	Radio frequency ablation
SCCA	Squamous cell carcinoma antigen
SGOT	Serum Glutamic-Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SMR	Standardized mortality ratio
TACE	Transcatheter arterial embolization
TGF- β	Transforming Growth Factor- β
TNF-α	Tumor necrosis factor alpha
TNM	Tumor node metastasis
UNOS	United Network for Organ Sharing
US	Ultrasound scanning
VCM	Vinyl chloride monomer
VEGF	Vascular endothelial growth factor
vs	Versus
WBCs	White Blood Cells

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Introduction

Hepatocellular carcinoma (HCC) is one of the commonest cancers worldwide. It is a major health problem and its incidence is increasing. The presence of cirrhosis of the liver is the major risk factor and worldwide this is largely due to chronic hepatitis C virus (HCV) and hepatitis B virus (HBV) infection. The diagnostic modalities, especially with respect to hepatic imaging, have improved in recent years. This, along with HCC surveillance in patients with cirrhosis, has led to the detection of HCC at an earlier stage, when curative therapy is likely to be more successful (***Gomaa et al., 2009).***

HCC is a major cause of morbidity and mortality: HCC is the seventh most common cancer worldwide, and the third leading cause of cancer-related deaths. In 2008, an estimated 748,000 new cases of liver cancer occurred and approximately 696,000 people died of this cancer worldwide, an increase from 626,000 new liver cancers and 598,000 deaths from liver cancer in 2002 **(*Ferlay* et al., 2010).**

Up to 80% of HCCs develop against a background of cirrhosis of the liver and while we believe that surveillance of the at risk cirrhotic population could aid earlier detection of the disease and decrease the cancer related mortality rate, our present success is limited by the lack of sensitive biomarkers **(Beale et al., 2008).**

Serum tumor markers have several potential uses: for early diagnosis of HCC in high risk patients, in determining prognosis, to estimate tumor volume as well as to monitor therapeutic response and detect recurrence **(Yoon, 2008).**