Evaluation of Serum Midkine as a Marker of Hepatocellular Carcinoma in Cirrhotic Egyptian Patients

A Thesis

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By

Mohamed Ramadan Osman

Bachelor Degree in Medicine and Surgery Ain Shams University

Supervised by

Prof.Dr. Noha Abdelrazek Elnakeeb

Professor of Internal Medicine and Gastroenterology
Faculty of medicine – Ain Shams University

Assist.Prof.Dr.Ahmed El Saady Mohammed Khayyal

Assistant Professor of Internal Medicine and Gastroenterology
Faculty of medicine – Ain Shams University

Dr. Ahmed Mohamed El Ghandour

Lecturer of Internal Medicine and Gastroenterology
Faculty of medicine – Ain Shams University

Faculty of Medicine
Ain Shams University
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بسم الله الرحمن الرحيم

﴿وَعَلَّمَكَ مَا لَمْ تَكُنْ تَعْلَمُ وَكَانَ فَضْلُ اللهِ عَلَيْكَ عَظِيمًا﴾

صدق الله العظيم

سورة النساء آية (١١٣)

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List of Abbreviations

Abb.	Full term
5`-NPD	*5`-Nucleotide phosphodiesterase*
8-OHDG	*8-hydroxydeoxyguanosine*
AASLD	*American Association for the Study of Liver Disease*
AFP	*Alfa feto protein*
AFPL3	*Agglutinin reactive AFP*
AFU	*Alpha L-Fucosidase*
Alb	*Albumin*
ALP	*Alkaline phosphatase*
ALT	*Alanine aminotransferase*
AST	*Aspartate aminotransferase*
BCLC	*Barcelona Clinic Liver Cancer*
BUN	*Blood urea nitrogen*
CEA	*Carcinoembryonic Antigen*
CLIP	*Cancer of the Liver Italian Program*
CT	*Computed tomography*
CUPI	*Chinese University Prognostic Index*
CYFRA21-1	*Cytokeratin 19 fragment*
D.Bil	*Direct bilirubin*
DCP	*Des-γ-carboxy prothrombin*
EASL	*European Association for the Study of the Liver*
ECG	*Electrocardiogram*
ELISA	*Enzyme Linked Immunosorbent assay*
GGT	*Gamma glutamyl transpeptidase*
GP73	*Golgi protein-73*
HBsAg	*Hepatitis B surface antigen*
HBV	*Hepatitis B virus*

List of Abbreviations Cont...

Abb.	Full term
HCC	*Hepatocellular carcinoma*
HCV	*Hepatitis C virus*
HDV	*Hepatitis D virus*
HGF	*Hepatocyte growth factor*
HNE	*4-hydroxynonenal*
HRP	*Horseradish Peroxidase*
HSP	*Heat shock protein*
ICC	*Intrahepatic cholangiocarcinoma*
IGF	*Insulin-like growth factor*
IGF-2	*Insulin Growth Factor-2*
IGF-II	*Insulin-like growth factor-II*
IL-8	*Interleukin-8*
INR	*International normalization Ratio*
JIS	*Japan Integrated Staging*
LCSGJ	*Liver Cancer Study Group of Japan*
MAGE-1	*Melanoma antigen gene*
MDK	*Midkine*
MFP	*Medial floor plate*
MR	*Magnetic resonance*
MRI	*Magnetic resonance imaging*
MWA	*Microwave ablation*
Na	*Sodium*
NAFLD	*Non alcoholic fatty liver disease*
OLT	*Orthotopic liver transplantation*
OS	*Overall survival*
PDGFR-beta	*Platelet-derived growth factor receptor beta*
PET	*Positron emission tomography*
PIVKA	*Prothrombin induced by vitamin K absence*

List of Abbreviations Cont...

Abb.	Full term
PT	*Prothombin time*
PTPζ	*Phosphatase-ζ*
PTT	*Partial thromboplastin time*
Raf/MEK/ERK	*Raf/mitgen-activated protein kinase /extracellular signal-regulated kinase*
RFA	*Radiofrequency ablation*
SCCA	*Serum squamous cell carcinoma antigen*
SHARP	*Sorafenib HCC assessment randomised Protocol*
SU	*Sunitinib malate*
T.Bil.	*Total bilirubin*
TACE	*Trans arterial chemoembolization*
TGF-β1	*Transforming growth factor-beta 1*
TIS	*Taipei Integrated Scoring System*
TKs	*Tyrosine kinases*
US	*Ultrasonography*
VEGF	*Vascular Endothelial Growth Factor*
VIP	*Vasoactive intestinal peptide*

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the second leading cause of cancer-related deaths. The number of deaths per year for HCC worldwide is similar to the incidence, with nearly 748300 new cases and 695900 deaths per year. HCC most often develops in patients with a history of cirrhosis due to chronic alcohol abuse, non-alcoholic fatty liver disease, or hepatitis C virus (HCV) infection ***(Izumi, 2010).***

Biomarkers that distinguish HCC from inflammation and cirrhosis are desperately needed in order to enhance prognosis of these patients.

Contributing to the poor prognosis of HCC is the lack of specific symptoms in the early stages of the disease. More than 60% of patients are diagnosed with late-stage disease after metastasis has occurred ***(Altekruse, 2009)***, resulting in an overall 5-year survival rate of < 16% ***(Siegel, 2013)***. In contrast, patients diagnosed with early stage disease have a relatively good prognosis, with a 5-year survival rate of > 70% ***(Takayama et al., 2008).***

The diagnosis of HCC without a pathological diagnosis can be achieved by assessing serum α-fetoprotein (AFP) levels and diagnostic imaging, such as computed tomography (CT) and magnetic resonance imaging (MRI) ***(Aghoram et al., 2012).***

The ideal HCC biomarker is one that enables clinicians to diagnose asymptomatic patients and can be widely used in a screening process. In general, a biomarker valuable for clinical use achieves a level of sensitivity and specificity of ≥ 90%, and is non-invasive and cost-effective to allow widespread use. The most desirable biomarker is therefore tumor-specific and easily detectable in bodily fluids, such as serum, plasma, and bile ***(Pepe, 2001).***

Midkine (MDK) is a heparin-binding growth factor that has been associated with tumor migration and proliferation ***(Muramatsu, 2010).*** Not surprisingly, MDK is often overexpressed in various human tumors, making it an attractive target in tumor detection and treatment ***(Muramatsu, 2002).*** A clinical study on a cohort of 388 HCC patients and 545 hospital enrollees diagnosed with other diseases identified MDK as a discriminating tissue and serum biomarker with better sensitivity (86.9%, serum MDK) than AFP (51.9%) ***(Zhu, 2013).***

Aim of the Work

To evaluate serum Midkine as a marker for Hepatocellular carcinoma in cirrhotic Egyptian Patients.

Chapter 1

HEPATOCELLULAR CARCINOMA

Hepatocellular carcinoma (HCC) is the fifth most common malignancy and the second leading reason of cancer-associated deaths around the world, and more than 600,000 deaths are reported internationally each year ***(Ferlay et al., 2015).*** HCC takes up 85%–90% of primary liver cancers with 500,000 new cases of HCC all over the world every year ***(Bozkaya et al., 2012).***

Incidence rates of the disease are increasing globally. In the United States, the incidence has doubled over the past 20 years ***(El-Serag et al., 2014).***

The risk for HCC is influenced by etiology, activity, and stage of underlying liver disease. Patients with liver cirrhosis due to chronic infection with hepatitis C virus (HCV) or hepatitis B virus (HBV) have the highest risk. The rising incidence in Western countries is mainly due to the still high prevalence of HCV-associated liver cirrhosis and the increasing number of patients with advanced steatohepatitis as hepatic manifestation of the metabolic syndrome ***(El-Serag et al., 2014).***

Several reports indicate that HCC in the setting of metabolic syndrome may also arise in the absence of cirrhosis; however, the exact proportions of this condition or its risk factors are still under investigation ***(Younossi et al., 2015).***

The main reasons for the high mortality rate of HCC patients are ascribed to the lack of effective treatments and the increasing resistance to conventional radiotherapy and chemotherapy ***(Whittaker et al., 2010).***

Despite substantial progress in understanding of the molecular pathogenesis of HCC, imaging techniques, and novel therapies (including targeted drugs), the overall prognosis of HCC patients is still poor. Tumor multiplicity, frequent vascular invasion, and accompanying cirrhosis are clinical features of HCC that lead to unsatisfactory outcomes. High rates of tumor recurrence and resistance to chemotherapeutic agents also make the management of HCC challenging. The poor outcome of patients with HCC is attributed to late detection, with more than two-thirds of patients diagnosed at advanced stages of the disease ***(Stravitz et al., 2008).*** However, a considerable improvement in survival has been observed (5-year survival up from 40% to 70%) when patients are diagnosed at an early stage and receive potentially curative therapy in the form of liver transplantation, surgical resection, or tumor ablation ***(Liu et al., 2004).***

Epidemiology

Liver cancer in men is the fifth most frequently diagnosed cancer worldwide. In women, it is the seventh most commonly diagnosed cancer and the sixth leading cause of cancer death. In the United States, liver cancer is the ninth