

# **Evaluation of $\beta$ 2-Microglobulin in Patients with Liver Cirrhosis and Hepatocellular Carcinoma**

## **Thesis**

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

# قَالَ

سُبْحَانَكَ لَا يَعْلمُ لَنَا  
إِلَّا مَا عَلِمْتَ إِنَّكَ أَنْتَ  
الْعَلِيمُ الْعَظِيمُ

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# LIST OF CONTENTS

Title	Page No.
Content .....	I
List of Abbreviations .....	II
List of Tables .....	V
List of Figures .....	VII
Introduction.....	1
Aim of the Work .....	3
Review of Literature	
▪ Chapter I : Liver Cirrhosis.....	4
▪ Chapter II :Hepatocellular Carcinoma .....	20
▪ Chapter III:β2-Microglobulin & HCC .....	50
Patients and Methods .....	64
Results.....	72
Discussion .....	80
Conclusion & Recommendation .....	85
Summary .....	86
References.....	88
Arabic Summary .....	--

# LIST OF ABBREVIATIONS

<b>Abbrev.</b>	<b>Full term</b>
<b>AASLD</b>	American Association of Study for the Liver Diseases
<b>AFP</b>	Alpha fetoprotein
<b>AIDS</b>	Acquired immunodeficiency syndrome
<b>AJCC</b>	American Joint Committee of Cancer
<b>ALT</b>	Alanine amino-transferase
<b>AST</b>	Aspartate amino-tranferase
<b>β2-MG</b>	β2-microglobulin
<b>BCLC</b>	Barcelona-Clínic Liver Cancer
<b>CEA</b>	Carcinoembryonic antigen
<b>CHC</b>	Chronic hepatitis C
<b>CLIP</b>	Cancer of the Liver Italian Program
<b>CMML</b>	Chronic myelomonocytic leukemia
<b>CSF</b>	Cerebrospinal fluid
<b>CT</b>	Computer Tomography
<b>CTP</b>	Child-Turcotte-Pugh score
<b>DCP</b>	Des-γ-Carboxy Prothrombin
<b>DRA</b>	Dialysis-related amyloid
<b>EASL</b>	European Association for the Study of the Liver
<b>ECM</b>	Extracellular matrix
<b>ECOG</b>	Eastern Cooperative Oncology Group system
<b>ELISA</b>	Enzyme-linked immunosorbent assay
<b>GGT</b>	Gamma glutamyl transferase
<b>GPC3</b>	Glypican-3

## **LIST OF ABBREVIATIONS (cont..)**

<b>Abbrev.</b>	<b>Full term</b>
<b>HBs Ag</b>	HBV surface antigen
<b>HBV</b>	Hepatitis B virus
<b>HCC</b>	Hepatocellular carcinoma
<b>HCV</b>	Hepatitis C virus
<b>HE</b>	Hepatic encephalopathy
<b>HGF</b>	Hepatocyte growth factor
<b>HIF-1<math>\alpha</math></b>	Hypoxia inducible factor-1 $\alpha$
<b>HLA</b>	Human leucocytic antigen
<b>IBD</b>	Inflammatory bowel disease
<b>IGF</b>	Insulin growth factor
<b>IL-6</b>	Interleukin-6
<b>INR</b>	International Normalization Ratio
<b>LC</b>	Liver cirrhosis
<b>MELD</b>	Model for End-stage Liver Disease
<b>MHC</b>	Major histocompatibility complex
<b>MOHP</b>	Ministry of Health and Population
<b>MRI</b>	Magnetic Resonance Imaging
<b>MSCs</b>	Mesenchymal stem cells
<b>NCCN</b>	National Comprehensive Cancer Network
<b>NIH</b>	National Institutes of Health
<b>PCR</b>	Polymerase Chain Reaction
<b>PELD</b>	Pediatric End-Stage Liver Disease
<b>PIVKA II</b>	Protein induced by vitamin K
<b>PSS</b>	Performance status score
<b>RCT</b>	Randomized Controlled Trial

## **LIST OF ABBREVIATIONS (cont..)**

<b>Abbrev.</b>	<b>Full term</b>
<b>RFA</b>	Radiofrequency ablation
<b>ROC</b>	Receiver operating characteristic
<b>SBP</b>	Spontaneous bacterial peritonitis
<b>SELDI-TOF-MS</b>	Surface-enhanced laser desorption ionization time-of-flight mass spectrometry
<b>SLE</b>	Systemic lupus erythematosus
<b>SOR</b>	Standard options and Recommendations
<b>TACE</b>	Transarterial Chemoembolisation
<b>TFR</b>	Transferrin receptor
<b>TFTFR</b>	Transferrin-transferrin receptor
<b>TGF- <math>\beta</math>1</b>	Transforming growth factor- $\beta$ 1
<b>TNM</b>	Tumor Node Metastasis
<b>UNOS</b>	United Network of Organ Sharing
<b>VEGF</b>	Vascular endothelial growth factor
<b>WHO</b>	World Health Organization



# LIST OF TABLES

Tab. No.	Title	Page No.
<b>Table (1):</b>	The Child's-Turcotte-Pugh (CTP) score.....	11
<b>Table (2):</b>	Mortality in Egypt due to liver disease, 2001-2006 .....	17
<b>Table (3):</b>	TNM Classification for HCC .....	40
<b>Table (4):</b>	Okuda staging system .....	41
<b>Table (5):</b>	Barcelona Clinic Liver Cancer staging for HCC .....	42
<b>Table (6):</b>	Performance status scores .....	43
<b>Table (7):</b>	CLIP score .....	44
<b>Table (8):</b>	comparison between the three studied groups as regards gender .....	72
<b>Table (9):</b>	Descriptive statistics of the mean age in the three studied groups .....	73
<b>Table (10):</b>	Comparison between the three studied groups as regards the mean level of $\beta$ 2- MG .....	73
<b>Table (11):</b>	Comparison between the three studied groups as regards liver function tests .....	74
<b>Table (12):</b>	Comparison between the three studied groups as regards the PT& INR .....	75

## LIST OF TABLES (cont..)

Tab. No.	Title	Page No.
<b>Table (13):</b>	comparison between the three studied groups as regards positivity of $\beta$ 2-MG (cut off value 3 mcg/ml).....	75
<b>Table (14):</b>	correlation coefficient between $\beta$ 2-MG level and liver function tests in group I .....	76
<b>Table (15):</b>	correlation coefficient between $\beta$ 2-MG level and AFP, number of tumor foci and tumor size .....	76
<b>Table (16):</b>	comparison between different child-paugh scores as regards positivity of $\beta$ 2-MG (cut off value 3 mcg/ml) in group II .....	77
<b>Table (17):</b>	correlation coefficient between $\beta$ 2-MG and liver function tests in group II .....	77
<b>Table (18):</b>	sensitivity and specificity of $\beta$ 2-MG in detection of HCC (considering healthy subjects as controls) .....	78
<b>Table (19):</b>	sensitivity and specificity of $\beta$ 2-MG in detection of HCC (considering patients with liver cirrhosis as controls) .....	79

# LIST OF FIGURES

Fig. No.	Title	Page No.
<b>Figure (1):</b>	Diagnostic algorithm and recall policy .....	31
<b>Figure (2):</b>	Updated BCLC staging system and treatment strategy .....	46
<b>Figure (3):</b>	The principle of the double antibody sandwich ELISA .....	67
<b>Figure (4):</b>	ROC curve for the sensitivity and specificity of $\beta$ 2-MG level in detection of HCC.....	78
<b>Figure (5):</b>	ROC curve for the sensitivity and specificity of $\beta$ 2-MG in detection of HCC (considering patients with liver cirrhosis as controls).....	79

# Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors worldwide. Patients with liver cirrhosis are at higher risk for the development of HCC. To date diagnostic imaging such as Computer Tomography or Magnetic Resonance Imaging (MRI) is taken as the gold standard for definitive diagnosis of HCC (*Yumi Saito et al., 2010*).

Several serum markers developed for the diagnosis of HCC.  $\alpha$ -fetoprotein (AFP) and protein induced by vitamin K absence (PIVKA-II) is most widely used as a diagnostic serum marker for HCC, however their early diagnostic value is poor (*Sherman, 2001*). Up to 40% of HCC patients have normal AFP. Moreover, AFP can also be elevated in patients with cirrhosis or exacerbation of chronic hepatitis. Prospective studies evaluating the value of AFP in HCC surveillance have reported sensitivities of 39-64%, specificity of 76-91% and positive predictive values of 9-32% (*Jorge A. Marrero, 2003*).

## Introduction

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$\beta$ 2-microglobulin ( $\beta$ 2-MG) is a non-glycosylated polypeptide composed of 99 amino acids. It is one of the components of major histocompatibility complex HLA class I molecules on the cell surface of all nucleated cells (*Yumi Saito et al., 2010*). Increased serum levels of  $\beta$ 2-MG occur in multiple myeloma, lymphoma, Sjogren's syndrome, amyloid fibrils and in patients receiving hemodialysis for long periods (*Ryu et al., 2006*). High serum levels of  $\beta$ 2-MG were also detected in many infectious diseases including infection with HCV (*Malaguarnera et al., 2000*).

A significant correlation was found between  $\beta$ 2-MG and interleukin-6 (IL-6), AFP and HCC tumor size. This indicates that the elevation of  $\beta$ 2-MG seems to be a consequence of the stimulation of hepatocytes by humoral components such as IL-6. Weakening of the immune system, due to IL-6, may be responsible for a more severe progression of HCC and overexpression of  $\beta$ 2-MG (*Saad et al., 2005*).

## **AIM OF THE WORK**

**The aim of the present study** was to verify the reliability of  $\beta$ 2-MG as a marker for diagnosis of HCC and its significance in evaluation of severity of liver cirrhosis.

## LIVER CIRRHOSIS

Liver cirrhosis is defined as the histological development of regenerative nodules surrounded by fibrous bands in response to chronic liver injury that leads to portal hypertension and chronic liver disease. Recent advances in the understanding of the natural history and pathophysiology of cirrhosis, and in treatment of its complications, resulted in improved management, quality of life and life expectancy of cirrhotic patients. Liver transplantation remains the only curative option for a selected group of patients, but pharmacological therapies that can halt progression to decompensated cirrhosis or even reverse cirrhosis are being developed (*Schuppan and Afdhal, 2008*).

Liver fibrosis occurs as a result of accumulation of extracellular matrix (ECM) proteins including collagen that occurs in most types of chronic liver diseases. Activated hepatic stellate cells, portal fibroblasts, and myofibroblasts of bone marrow origin have been identified as major collagen-producing cells in the injured liver (*Friedman, 2003*).