Evaluation of ß2-Microglobulin in Patients with Liver Cirrhosis and Hepatocellular Carcinoma

Thesis

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By

Mohamed Fouad Mohamed Ali Gomaa
M.B.B.CH
Faculty of Medicine- Ain Shams University

Under Supervision of

Prof. Dr. Sameh Mohamed Ghaly
Professor of Internal Medicine
Faculty of Medicine-Ain Shams University

Prof. Dr. Reham Ezzat Al Swaff
Assistant Professor of Internal Medicine
Faculty of Medicine-Ain Shams University

Dr. Hosam Samir Elbaz
Lecturer of Internal Medicine
Faculty of Medicine-Ain Shams University

Faculty of Medicine
Ain Shams University
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Thank you

Mohamed Fouad

LIST OF CONTENTS

LIST OF ABBREVIATIONS

Abbrev.	Full term
AASLD	American Association of Study for the Liver Diseases
AFP	Alpha fetoprotein
AIDS	Acquired immunodeficiency syndrome
AJCC	American Joint Committee of Cancer
ALT	Alanine amino-transferase
AST	Aspartate amino-tranferase
ß2-MG	ß2-microglobulin
BCLC	Barcelona-Clínic Liver Cancer
CEA	Carcinoembryonic antigen
CHC	Chronic hepatitis C
CLIP	Cancer of the Liver Italian Program
CMML	Chronic myelomonocytic leukemia
CSF	Cerebrospinal fluid
CT	Computer Tomography
CTP	Child-Turcotte-Pugh score
DCP	Des-γ-Carboxy Prothrombin
DRA	Dialysis-related amyloid
EASL	European Association for the Study of the Liver
ECM	Extracellular matrix
ECOG	Eastern Cooperative Oncology Group system
ELISA	Enzyme-linked immunosorbent assay
GGT	Gamma glutamyl transferase
GPC3	Glypican-3

LIST OF ABBREVIATIONS (cont..)

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

LIST OF ABBREVIATIONS (cont..)

Abbrev.	Full term
RFA	Radiofrequency ablation
ROC	Receiver operating characteristic
SBP	Spontaneous bacterial peritonitis
SELDI-TOF-MS	Surface-enhanced laser desorption ionization time-of-flight mass spectrometry
SLE	Systemic lupus erythematosus
SOR	Standard options and Recommendations
TACE	Transarterial Chemoembolisation
TFR	Transterrin receptor
TFTFR	Transferrin-transferrin receptor
TGF- β1	Transforming growth factor- β1
TNM	Tumor Node Metastasis
UNOS	United Network of Organ Sharing
VEGF	Vascular endothelial growth factor
WHO	World Health Organization

LIST OF TABLES

LIST OF TABLES (cont..)

LIST OF FIGURES

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. α –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).***

ß2-microglobulin (ß2-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 ß2-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 ß2-MG were also detected in many infectious diseases including infection with HCV ***(Malaguarnera et al., 2000)***.

A significant correlation was found between ß2-MG and interleukin-6 (IL-6), AFP and HCC tumor size. This indicates that the elevation of ß2-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 ß2-MG ***(Saad et al., 2005)***.

AIM OF THE WORK

The aim of the present study was to verify the reliability of ß2-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).***