شبكة المعلومات الجامعية

التوثيق الإلكتروني والميكروفيلم

بسم الله الرحمن الرحيم

HANAA ALY

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جامعة عين شمس

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قسم

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Evaluation of some biomarkers for hepatocellular carcinoma prognosis in chronic hepatitis C patients

ATHESIS

Submitted for the a word of Ph.D. Degree in Science in Zoology

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AIN SHAMS UNIVERSITY
FACULTY OF SCIENCE
ZOOLOGY DEPARTMENT

2020

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صدق الله العظيم

سورة الضحى: (٥)

Acknowledgements

I would like to express my deepest gratitude and appreciation to ***Professor Ahmed Refaat Ezzat,*** *Professor of Physiology, Zoology Department, Faculty of Science, Ain Shams University for supervising this work. I especially appreciate his constructive criticism, critical reading, and significant contribution to the manuscript writing and preparation.*

My deepest thanks to ***Professor Hoda Gamal El-Din Hegazy,*** *Professor of Physiology, Zoology Department, Faculty of Science, Ain Shams University, for her valuable suggestions, constant advice and follow up throughout this work. I appreciate her patience and understanding in guiding me to complete this dissertation successfully.*

I would also like to express my deepest thanks to ***Professor Wafaa Shousha,*** *Professor of Biochemistry, Chemistry Department, Faculty of Science, Helwan University for her support and help in every detail I needed to write and prepare this manuscript. I strongly value her suggestions and guidance without which, this work would have not been possible.*

I am also thankful to ***Dr. Amal Ahmed Mohamed,*** *Associate Professor of Biochemistry, National Hepatology and Tropical Medicine Research Institute for the help and support she generously provided throughout the practical work. Her eagerness to transfer her illustrious experience to me made it possible to accomplish the vast number of laboratory investigations that were necessary to compile this study.*

ABSTRACT

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Hepatocellular carcinoma (HCC) is one of the most prevalent types of cancer and represents the third leading cause of cancer deaths worldwide. HCC is highly correlated to chronic inflammation or cirrhotic liver caused by hepatitis viral infection or other types of tissue assault leading to liver damage. In Egypt, HCC represents the second most common type of cancer in men, whereas it ranked as the 6th most common cancers in women. Early diagnosis of hepatocellular carcinoma (HCC) remains a challenge and diagnosis is usually achieved by measurement of biomarkers. The heterogeneous nature of HCC makes it difficult to agree on a perfect single biomarker for this tumor. Consequently, the diagnostic and predictive potentials of biomarkers widely used in clinical practice are limited. There is a general consensus on the need to look for more reliable biomarkers, or a combination of biomarkers in conjunction with clinical investigations to improve the specificity, sensitivity, and predictivity. The objective of the present study is to assess a panel of biomarkers that can significantly increase both the specificity and sensitivity to diagnose the prognosis of HCV-related HCC. For this purpose, a group of biomarkers which have been used on a wide scale in clinical practice, in addition to two suggested novel ones; the vascular adhesion molecule-1 (VCAM-1) and soluble platelet endothelial cell adhesion molecule-1 (sPECAM-1) were evaluated in Egyptian patients with chronic hepatitis C and hepatocellular carcinoma. The ROC analyses were also applied to evaluate the specificity and sensitivity of these chosen biomarkers in an attempt to reach a recommendation for the employment of these markers to predict early development of hepatitis C to hepatocellular carcinoma. In the present study, 120 individuals from the National Hepatology and Tropical Medicine Research Institute, enrolled during the period from September 2014 to March 2017, were divided into four major groups; the control group which comprised 20 individuals. HCV group comprising 50 patients with chronic hepatitis C genotype 4,

HCC group comprising 25 patients with hepatocellular carcinoma without HCV, and finally the HCC+HCV group comprising 25 patients with proven chronic hepatitis C genotype 4 and developed hepatocellular carcinoma. All the patients were subjected to laboratory investigations included liver function tests, oxidative stress markers, determination of AFP, IL-10, IL-6, IL-8, TNF-α, IFN-γ, MCP-1, VCAM-1 and sPECAM-1, serum level, as well as the LDH and caspase-3 activities, in order to predict the early development of hepatitis C into hepatocellular carcinoma. The results revealed significant differences in most of the liver function indicators, LDH activity, oxidative stress markers, IL-8, TNF-α, MCP-1 and AFP between healthy individuals and diseases groups. There was no relation between serum IL-6, IL-10, INF-γ, sVCAM-1, sPECAM-1, caspase-3 and the HCV or HCC cases. From the ROC curve analysis results, it was found that sPECAM-1 and sVCAM-1 were not sensitive or specific biomarkers for HCC. Serum AFP levels were high specific, but insufficiently sensitive to detect HCC.

In conclusion, relying on a single biomarker for the diagnosis of HCC is not possible by employing the currently used markers in diagnostic practice. Serum PECAM and serum VCAM were not sensitive indicators for HCC diagnosis because of their low discriminative power between groups as the ROC test disclosed. Consequently, they were not reliable with respect to their predictive power in the progression of HCV-related HCC development when used separately or together. On the other hand, this study provided a comprehensive evaluation of the efficiency of several widely used biomarkers which will significantly contribute to the pursuit of the ideal panel of biomarkers for HCC diagnosis and prognosis.

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LIST OF ABBREVIATIONS

Abbreviation	Meaning
AFP	Alpha-fetoprotein
AFP-L1	Alpha-fetoprotein lectin glycoform 1
AFP-L2	Alpha-fetoprotein lectin glycoform 2
AFP-L3	Alpha-fetoprotein lectin glycoform 3
ALT	Alanine aminotransferase
AMPK	Activated protein kinase
ANOVA	Analysis of variance
ASSLD	American Association for the Study of Liver Diseases
AST	Aspartate aminotransferase
AUC	Area under curve
BAK	BCL-2 antagonist killer 1
BAX	BCL-2- associated X protein
BCG	Bromocresol green
BCL-2	B-cell lymphoma 2
BCLC	Barcelona Clinic Liver Cancer
BMI	Body mass index
CAMS	Cell adhesion molecules
Caspase-3	Cysteine aspartic acid protease

Abbreviation	Meaning
CD8	Cluster of differentiation 8
CHC	Chronic hepatitis C
CLIP score	Cancer of the Liver Italian Program
CRP	C-reactive protein
CT	Computerized tomography
CTLs	Cytotoxic T lymphocytes
DAAs	Direct-acting Antiviral Agents
DC	Dendritic cells
DCs	Dendrite cells
DNA	Double strand nucleic acid
DPD	Dichlorophenyldiazonium tetrafluoroborate
DTNB	5,5-dithio-bis-(2-nitrobenzoic acid)
EC	Endothelial cells
ELISA	The enzyme-linked immunosorbent assay
FasL	Fas ligand
FPR	False positive rate
GBD	The Global Burden of Disease study
GCS-HS	Glutamylcysteine synthetase heavy subunit
GGT	Gamma glutamyl transferase

Abbreviation	Meaning
GPX	Glutathione peroxidase
GR	Glutathione reductase
GSH	Reduced glutathione
GSSG	Oxidized glutathione
GTP	Guanosine-5'-triphosphate
GTs	Genotypes
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C viral
HIF	Hypoxia-inducible factors
HS	Heparin sulphate
HSCs	Hepatic stellate cells
ICAM-1	Intercellular adhesion molecule-1
IFCC	International Federation for Clinical Chemistry
IFN-γ	Interferon gamma
IL-1	Interleukin-1
IL-10	Interleukin-10
IL-4	Interleukin-4