

**Study of Serum Vascular Endothelial Growth
Factor Versus Alpha Fetoprotein In HCV Cirrhotic
Patients with Hepatocellular Carcinoma (HCC)
Before and after Therapeutic Intervention**

Thesis

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List of Abbreviations

AAT	:	Alpha one anti-trypsin
AFP	:	Alpha-feto protein
AGP	:	Alpha one acid glycoprotein
AJCC	:	American Joint Committee On Cancer
ALP	:	Alkaline phosphatase
APC	:	Adenomatous polyposis coli
BCLC	:	Barcelona Clinic Liver Cancer
Bil	:	Billirubin
BMP	:	Bone morphogenic protein
CLIP	:	Cancer of Liver Italian Program
CT	:	Computed tomography.
DCP	:	Desgamma carboxy prothrombin
DKK1	:	Dickkopf 1
ECOG	:	Eastern cooperative oncology group
EGF	:	Epidermal growth factor
EGFR	:	Epidermal growth factor receptor
EpCAM	:	Epithelial cell adhesion molecule
ERK	:	Extracellular signal-regulated kinase
EUS	:	Endoscopic ultra sonography
FDG	:	Fluorodeoxyglucose
FGF	:	Fibroblast growth factor
FLK-1	:	Fetal liver kinase
FLT-1	:	Fms-like tyrosine kinase
GDP	:	Guanosine 5'-diphosphate
GGT	:	Gamma-glutamyl transpeptidase

List of Abbreviations (Cont.)

GLYP3	:	Glypican-3
GP73	:	Golgi protein 73
HCC	:	Hepatocellular carcinoma
HIFU	:	High intensity focus ultrasound
HSP70	:	Heat shock protein 70
IGF	:	Insulin like growth factor
IL-1	:	Interlukin-1
IR	:	Insulin receptor
JIS	:	Japan Integrated Staging score
K19	:	Keratin 19
LFT	:	Liver function tests
MELD	:	Model for endstage liver disease
miR	:	Micro RNA
MRI	:	Magnetic resonance imaging.
m-RNA	:	Messenger RNA
MSCT	:	Multi-Slice CT
NAFLD	:	Nonalcoholic fatty liver disease
NASH	:	Nonalcoholic steatohepatitis
NK cells	:	Natural killer cells
OPN	:	Osteopontin
PEI	:	Percutaneous ethanol injection
PIVKA II	:	Prothrombin induced by Vitamin K Absence II
PLGF	:	Placental growth factor
PT	:	Prothrombin time
PVT	:	Portal vein thrombosis
RCT	:	Randomized control trial
RFA	:	Radiofrequency ablation
TACE	:	Transarterial chemoembolization
TAE	:	Trans arterial embolization
TE	:	Transient elastography
TGF	:	Transforming growth factor

List of Abbreviations (Cont.)

US	:	Ultrasonography
VEGF	:	Vascular endothelial growth factor
VEGF	:	Vascular endothelial growth factor
VEGFR	:	Vascular Endothelial Growth Factor Receptors

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Introduction

Liver cirrhosis is considered a premalignant state, as about 80% of hepatocellular carcinoma(HCC) is associated with liver cirrhosis (**Yagmur et al., 2007**).Cirrhosis is the strongest and the most common known risk factor for hepatocellular carcinoma (HCC) ,especially cirrhosis related to hepatitis C virus (HCV) and hepatitis B (HBV) infections (**Yagmur et al., 2007**).

Hepatocellular carcinoma (HCC) is one of the most common and lethal cancers in the world. More than one million cases of HCC occur in the world each year (**Jain et al., 2010**), (**Paul et al., 2009**)

Approximately 80% of HCC cases arise in developing countries. In Egypt, there is a rising trend of HCC as there was nearly a two fold increase of the proportion of HCC among chronic liver disease patients over the last decade (**El-Zayadi et al., 2005**).

Although many treatment modalities for HCC are available (including hepatic resection, liver transplantation, radiofrequency ablation, transarterial chemoembolization, etc.) at present, the prognosis of HCC patients remains dismal because it is detected at an advanced, non-resectable stage (**Padma et al., 2009**)

The diagnosis of HCC is mainly based on a combination of abdominal ultrasound and serum alpha fetoprotein level. However, tumors that are too small will be missed by abdominal ultrasound and serum alpha fetoprotein level which lacks organ and tumor specificity and has low sensitivity particularly in early stage disease (**Padma et al., 2009**).

Clearly, the available screening methods are inadequate for early detection and follow up of HCC, so there is need for other markers have to high sensitivity in early diagnosis of HCC as well as the specificity in differentiation between HCC and benign lesions (**Padma et al., 2009**).

Early diagnosis of HCC can improve the prognosis of HCC patients. Many research groups are evaluating the sensitivity of available tumor markers and also are investigating the development of novel markers. The primary marker for HCC is alpha fetoprotein (AFP), a single polypeptide chain glycoprotein. Generally, AFP shows acceptable sensitivity; however, AFP is not secreted in all cases of HCC and may be normal in as many as 40% of patients with early HCC (**Nakatsura et al., 2003**). In addition, the serum AFP level does not always correspond to the clinical stage of HCC (**Nakagawa et al., 1999**). Thus, AFP appears to have limited utility as a screening test (**Bruix and Sherman, 2005**).

Therefore, the diagnostic sensitivity and specificity of AFP are unsatisfactory and questionable. It is thus necessary to select other specific methods for the diagnosis of HCC. (**Stefaniuk et al.,2010**).

Serum vascular endothelial growth factor (VEGF) levels in HCC patients were significantly higher, compared to control individuals, and was correlated with venous invasion and advanced tumor stage. They concluded that the expression of VEGF in HCC tissues was correlated with AFP (**Amaoka et al., 2007**).

Furthermore, this biomarker was related to invasiveness and metastasis of HCC (**Amaoka et al., 2007**).

The expression of VEGF in HCC patients with microscopic venous invasion was significantly higher than that in HCC patients without microscopic venous invasion **(Huang et al., 2005)**

Human HCC is also a highly angiogenic tumor with several studies showing a strong correlation between tissue VEGF levels and HCC **(Semela and Dufour, 2004)**.

The elevation of VEGF in blood implies a promotion of tumor angiogenesis, and several studies have revealed the predictive value of circulating VEGF level in tumor progression and prognosis in various types of cancer **(Semela and Dufour, 2004)** .

Tumor VEGF levels correlate with increased microvessel density, which in turn is associated with vascular invasion, and higher recurrence risk **(Tseng et al., 2008)**.

So, the serum VEGF level in HCC patients is directly correlated with the metastasis and recurrences of tumors and increase gradually with the progression of HCC. The earlier the HCC metastasis, the higher the VEGF expression **(Zhao et al., 2003)**.

Therefore, the pretherapeutic serum VEGF level in HCC patients appears to reflect the diseases potential activity of vascular invasion and metastasis **(Zhao et al., 2003)**.

Aim of the work

The aim of the present work is:

- To study the clinical significance of serum VEGF in hepatitis C cirrhotic patients with HCC as a diagnostic marker before intervention and a prognostic marker after intervention to improve the outcome of HCC diagnosis and treatment
- To study the VEGF correlation with hepatocellular carcinoma in hepatitis C cirrhotic patients as a simple non invasive tool.