Relation between serum level of interleukin 6 and Cachexia in patients with post HCV Hepatocellular carcinoma

Thesis
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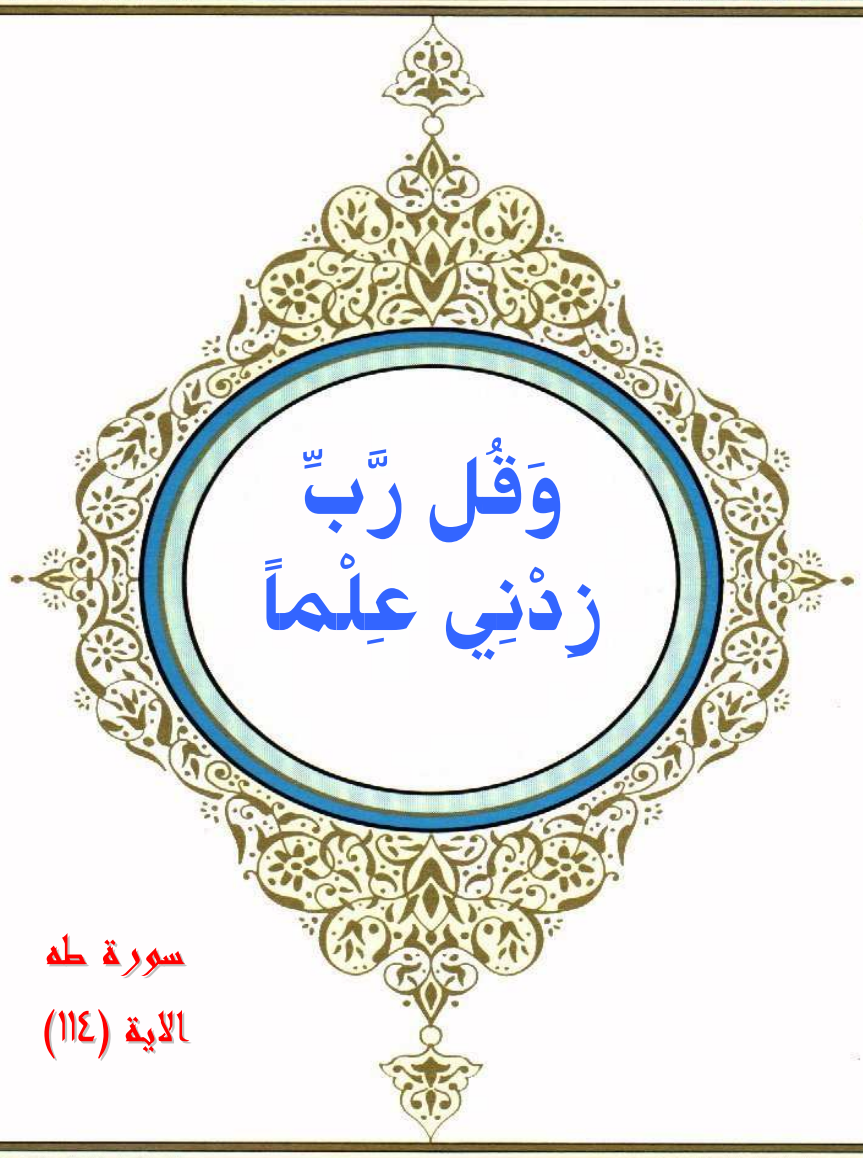

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List of Abbreviations

AASLD	American Association for the Study of Liver Diseases
AFB1	Aflatoxin B1
AFP	Alpha fetoprotein
AFP-L3	Lens culinaris agglutinin reactive fraction of AFP
Alb	S. albumin
ALT	S. alanine aminotransferase
AMI	Acute myocardial infarction
APPR	Acute phase protein response
AST	S.aspartate aminotransferase
AUROC	Area under the receiver operating characteristic curve
BCLC	Barcelona-Clinic Liver Cancer
BCP	Basal core promoter
BMI	Body mass index
BUN	Blood urea nitrogen
CAH	chronic active hepatitis
CBC	Complete blood count
CC	Cancer with cachexia
CNC	Cancer without cachexia
CNTF	Ciliary neutrophilic factor

CRP	C-Reactive Protein
CT	Computed Tomography
CT-1	Cardiotrphin-1
D.Bil	S.direct bilirubin
DCP	Des-gamma-carboxy-prothrombin
DFS	Disease-free survival
EBV	Ebstein-barr virus
EPA	Eicosapentaenoic acid
ESR	Erythrocyte sidemention rate
FFM	Fat-free mass
Hb	Hemoglobin
HBcab	Hepatitis B core antibody
Hbsag	Hepatitis B surface antigen
HBV	Hepatitis B virus infection
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
HH	Hereditary Hemochromatosis
HRT	Hormone replacement therapy
ICC	Intrahepatic cholangiocarcinoma
IDU	Intravenous drug use

IL-1	Interleukin-1
IL-6	Interleukin-6
INR	International normalized ratio
K	Potassium
LIF	Leucocyte inhibiting factor
LMF	Lipid mobilising factor
LSM	Liver Stiffness Measurement
MC3R	Melanocortin-3 receptors
MC4R	Melanocortin- 4 receptors
MSH	Melanocyte-stimulating hormone
MUAC	Mid upper arm muscle circumference
Na	Sodium
NAFLD	Non-alcoholic fatty liver disease
NAS	Non-alcoholic steatohepatitis
NKC	Natural killer cell
ONSs	Oral nutritional supplements
OSM	Oncostatin M
P.T	Prothrombin time
PAF	Platelet activating factor
PARs	Population Attributable Risks
PBMCs	Peripheral Blood Mononuclear Cells

PCR	Polymerase chain reaction
PIF	Proinflammatory factor
Plt	Platelet
PTH	Parathyroid hormone
RCTs	Chemotherapy/radiotherapy Treatments
RFA	Radiofrequency ablation
S.Alb	Serum albumin
S.creat	Serum creatinine
SIR	Standard incidence ratio
S.Urea	Serum urea
T.Bil	S.total bilirubin
T.P	S. total protein
TACE	Transarterial chemoembolization .
TAE	Arterial embolization
TNF	Tumour necrosis factor
US	Ultrasonography
WBcs	White blood cells
Wt	Weight
αFP	Alpha-fetoprotein

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Introduction

Cachexia due to cancer is one of the most frequent features of malignancy (**Loberg et al., 2007**), it accounts for up to 30-50% of cancer-related deaths in gastrointestinal tract malignancies (**Polesty & Dudrick , 2003**).

Cachexia correlates with poor performance status, poor quality of life, and a high mortality rate in cancer patients (**Dewys et al., 1980**). In a meta-analysis of studies pertaining to patients with advanced cancer and survival of less than 90 days, symptoms including weight loss and anorexia correlated with poor prognosis (**Maltoni et al., 2005**). Loss of greater than 5–10% of body weight is usually taken as a defining point for Cachexia, although the physiological changes may be present long before this cutoff point is reached. Furthermore, the degree of weight loss which significantly impacts on prognosis or performance has not been defined (**Maltoni et al., 2005**).

Cachexia due to cancer is a complex metabolic disorder, including loss of adipose tissue due to lipolysis, loss of skeletal muscle mass, elevation of resting energy consumption, anorexia, and reduction of oral food intake (**Chamberlain, 2004**).

Despite intensive studies that have been conducted thus far in this field, the multifactorial pathological mechanism of cancer-related cachexia has not been fully exhibited, besides, currently available treatment modalities remain profoundly unsatisfactory (**Boddeart et al., 2006**). Nevertheless, it is well known that cytokine up-regulation contributes to involuntary weight loss, which is a hallmark of cancer- related cachexia (**Saini et al., 2006**).

Although the catabolism is mainly mediated by the effects of certain cytokines, such as tumor necrosis factor-a (TNF-a), interleukin-1β (IL-1β), and interleukin-6 (IL-6) (**Deans& Wigmore, 2005**), the mechanisms associated with cancer related anorexia are still not elucidated completely (**Ramas et al., 2004**). Previous studies concerning cachexia in gastrointestinal cancer revealed that other proinflammatory cytokines, such as IL-8 and, probably, vascular endothelial growth factor-A (VEGF-A) and midkine, might be involved in the process of cachexia (**Krzystek-Korpacka et al., 2007).**

A number of neuroendocrine factors appear to be dysregulated in the cancer state resulting in insulin resistance, reduced anabolic activity, and elevated cortisol. This dysregulation may be driven by the systemic inflammatory response associated with cancer. The endogenous production of or response to anabolic growth

factors in patients may be affected either by the tumour or the host response to the tumour and may contribute to Cachexia (**Skipworth et al., 2007**).

Tumor necrosis factor-alpha and the tumour factor proteolysis-inducing factor are the major contenders for skeletal muscle atrophy in cachectic patient. They both increase protein degradation and depress protein synthesis (**Tisdale, 2010**). Weight loss has been indicated as an important prognostic factor for cancer patients. Not only did weight loss predict overall survival, but it also indicated a trend towards lower chemotherapy response rates. cachexia contributes substantially to morbidity in cancer patients. It is associated with symptoms such as fatigue, weakness, poor physical performance, and thus leads to a lower self-rated quality of life. Indeed, when the impact of various factors is related to self-rated quality of life scores, the proportion determined by weight loss is 30% and by nutritional intake 20%, compared to cancer location (30%), disease duration (3%), and stage (1%) (**Ravasco et al., 2004**). Patients who continue to lose weight while receiving palliative chemotherapy have reduced global quality of life and performance scores when compared to those whose weight loss stabilises (**Persson & Glimelius, 2002**).

The strong impact that cancer cachexia has on cancer patients' outcome and quality of life suggests that nutritional issues should be taken into consideration from the beginning of the natural history of cancer; a concept termed the parallel pathway (**Muscaritoli et al., 2008**).

It was found that the production of IL-6 by Peripheral Blood Mononuclear Cells (PBMCs) in pancreatic cancer patients induced an acute phase protein response in another study (**O'Riordain et al., 1999**).

Martignoni et al., (2005) have suggested that IL-6-overexpression in cachectic pancreatic cancer patients is related to the ability of IL-6 producing tumours to sensitize PBMC and induce IL-6 expression in PBMCs. Some initial studies showed that drugs as EPA (eicosapentaenoic acid) can produce anabolic effects, principally gains of lean body mass, improvements in grip strength, quality of life, and reductions in IL-6 in a variety of cancers including pancreatic cancer (**Barber et al., 1999**), lung cancer and colorectal cancer (**Guarcello et al., 2007**).