#### Interleukin 18 as a serum marker in liver cirrhosis

**Thesis** 

Submitted for partial fulfillment of

The Master Degree in Internal Medicine

Presented by

**Marwa Monir Aziz** 

M.B., B.CH

Supervised by

Professor/ Khaled Mohamed Abd El Wahab

Professor of Internal Medicine

Faculty of Medicine, Ain Shams University

Professor/ Ehab Hassan Nashaat

Professor of Internal Medicine

Faculty of Medicine, Ain Shams University

Assistant professor/ Amir Helmy Samy

Assistant professor of Internal Medicine

Faculty of Medicine, Ain Shams University

**Faculty of Medicine** 

**Ain Shams University** 

2012

## <u>Acknowledgement</u>

First and foremost thanks to **God**, The most merciful.

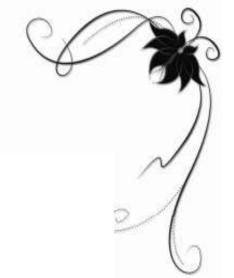
I wish to express my deep appreciation and sincere gratitude to **Prof.Dr. Khaled Abd ElWahab** for continuous help and guidance. He has generally devoted much of his time for supervising this study.

I am also very grateful to **Prof.Dr.Ehab Nashaat** for his generous help and guidance and also for his endless efforts for planning and supervising of this study. It was a great honor for me to work under his supervision.

I sincerely thank Ass.Prof.Dr.Amir Helmy for his guidance, support and revision of the whole study. This work would have not been possible without his sincere and generous help.

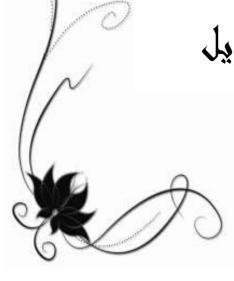
Marwa Monir Aziz





# داعما

المدي هذة الرسالة الي أمي و أخي ، فبدون محبتهما و مساندتهما السادقة ما السادقة ما كانت المما مني كانت الكتملت. الهما مني وافر الامتنان و جزيل



## **Contents**

•	Acknowledgement	I
•	Contents	II
•	List of Tables	III
•	List of Figures	IV
•	List of Abbreviations	V
•	Introduction	VI
•	Aim of the work	VII
•	Review of literature	
C	Chapter (1): Liver cirrhosis.	1
C	Chapter (2): New serum biomarkers of liver cirrhosis	46
C	Chapter (3): Interleukin 18	57
•	Patients and methods	77
•	Results	84
•	Discussion	115
•	Summary and Conclusion	123
•	Recommendations	125
•	References	126
•	Arabic Summary.	

### • List of tables:

TABLE NO	DISCRIPTION	PAGE NO
Table 1.1	Etiological classification of liver cirrhosis.	3
Table 1.2	Clinical effects of hepatitis viruses in USA.	12
Table1.3	Risk and predictive values in patients with cirrhosis and ascites regarding development of HRS.	25
Table 1.4	METAVIR score that is used to determine degree of fibrosis in HCV positive subjects.	33
Table 1.5	Child-Turcotte-pugh classification.	36
Table 2.1	Cytokines of innate immunity	53
Table 2.2	Cytokines of adaptive immunity	54
Table 3.1	Functional effects of IL-18.	61
Table R.1	Statistical differences between the studied groups according to different parameters	85
Table R.2	Demography of the studied groups according to Gender	86
Table R.3	Comparative study between serum level of IL-18 and Gender in the studied groups	88

Table R.4	Correlation between age and serum IL-18 in the studied groups	90
Table R.5	Correlation between total bilirubin and serum IL-18 in the studied groups	91
Table R.6	Correlation between serum albumin and serum IL-18 in the studied groups	93
Table R.7	Correlation between PT and serum IL-18 in the studied groups	95
Table R.8	Comparison between severity of ascites as regard IL-18 level in group 1.	97
Table R.9	comparison between grades of Child-Pugh classification as regard serum level of IL- 18 in group 1	99
Table	Correlation between serum creatinine and	
R.10	serum IL-18 in the studied groups.	101
Table	Correlation between AST and serum IL-18	103
R.11	in the studied groups.	
Table	Correlation between ALT and serum IL-	
R.12	18 in the studied groups	105
Table R.13	Comparison between METAVIR and serum IL-18 in HCV positive patients in group 1.	107

Table	Correlation between platelet count and	109
R.14	serum IL-18 in the studied groups	
Table	Correlation between the presence of viral	
R.15	hepatitis and the serum level of IL-18 in group 1.	111
Table	Comparison between viral hepatitis	113
R.16	phenotypes as regard serum level of IL-18	
	in group 1.	

# • List of figures:

FIG NO	DISCRIPTION	PAGE NO
Fig 1.1	Anatomy of the liver.	1
Fig R.1	Demography of the studied groups according to sex	87
Fig R.2	Comparative study between serum level of IL-18 and Gender in Group I	89
Fig R.3	Comparative study between serum level of IL-18 and Gender in Group 2	89
Fig R.4	Correlation between total bilirubin and serum IL-18 in group I	92
Fig R.5	Correlation between serum albumin and serum IL-18 in group I	94
Fig R.6	Correlation between PT and serum IL-18 in group I	96
Fig R.7	Comparison between severity of ascites as regard serum IL-18 in group 1	98
Fig R.8	Comparison between grades of Child-Pugh classification as regard serum level of IL-18 in group 1.	100
Fig R.9	Correlation between serum creatinine and serum IL-18 in the studied groups	102
Fig R.10	Correlation between AST and serum IL-18 in group I	104
Fig R.11	Correlation between ALT and serum IL-18 in group I	106
Fig R.12	Comparison between METAVIR score and serum IL-18 in HCV positive patients in group 1	108

Fig R.13	Correlation between platelet count and serum IL-18 in group I	110
Fig R.14	correlation between the presence of viral hepatitis and the serum level of IL-18 in group 1	112
Fig R.15	Comparison between viral hepatitis phenotypes as regard serum level of IL-18 in group 1	

### • List of abbreviations:

Atopic dermatitis.
Alkaline phosphatase
Alanine transaminase
Adult onset still's disease.
Aspartate aminotransferase
Binding protein.
Alpha cluster of differentiation number 40.
Color-encoded duplex sonography.
Chronic obstructive pulmonary disease.
Colony stimulating factor
Computed tomography
Epithelia growth factor
Enhanced Liver Fibrosis.
Erythropoietin
Fas ligand.
Fibroblastic growth factor.
FibroTest
Gastric antral vascular ectasia.
Granulocyte-CSF
Gamma glutamyl transferase.

GM-CSF	Granulocyte macrophagecolony stimulating factor.
GOT	Serum glutamic oxaloacetic transaminase
GPT	Serum glutamic pyruvic transaminase
GTP	Guanosine-5'-triphosphate.
HCC	Hepatocellular carcinoma
HDL	High-density lipoprotein
HHV-6	Human Herpesvirus 6.
HRS	Hepatorenal syndrome
HVPG	Hepatic venous pressure gradient.
IBD	Inflammatory bowel disease.
ICE	interleukin-1 beta converting enzyme
ICSBP	Interferon consensus sequence-binding protein.
IG	Immunoglobulin.
IGF1	Insulin-like growth factor 1
IGIF	interferon gamma inducing factor
IL	Interleukin.
IL-R	Interleukin receptor.
INR	International normalization ratio.
IRAK	IL-1R-associated kinase
LCAT	Lecithin-cholesterol acyltransferase
LDL	low-density lipoprotein

MAPK	Mitogen-activated protein kinases.
M-CSF	Monocyte-CSF.
MELD	Model for End-Stage Liver Disease.
MetS	Metabolic syndrome.
MMP	Matrix metalloproteinases.
MRI	Magnetic resonance imaging
mRNA	Messenger Ribonucleic acid.
NK	Natural killer cells.
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NSAIDs	Nonsteroidal anti-inflammatory drugs.
PBMCs	Peripheral blood mononuclear cell.
PDGF	platelet-derived growth factor
PEM	Protein-energy malnutrition.
PPH	Porto pulmonary hypertension
PRIME	Prospective Epidemiological Study of
study	Myocardial Infarction.
PT	Prothrombin time.
rIL-18	Recombinant protein interleukin 18.
SCF	Stem cell factor.
SLE	systemic lupus erythematosus
TGF	Transforming growth factor

TGFβ1	transforming growth factor beta 1
Th1	T helper cell type 1.
TIMP	Tissue inhibitors of metalloproteinases.
TNFα	tumor necrosis factor-alpha
TRAF6	Tumor necrosis factor receptor-associated factor 6.
VEGF	Vascular endothelia cell growth factor
VLDL	Very low-density lipoprotein.
γ-GT	Gamma-glutamyltransferase

## Aim of the work

The aim of this work is to study the serum level of interleukin 18 in patients with liver cirrhosis and its role in the diagnosis and prognosis of the disease.

#### **Introduction**

Liver cirrhosis is a progressive, irreversible, chronic disease of the liver, involving the whole organ as a consequence and final stage of various chronic liver diseases of different etiology or the result of long-term exposure to various toxins. (**Zeisberg et al.**, **2007**).

Liver biopsy is considered the gold standard for assessing fibrosis and inflammation of the liver. Given the limitations of the liver biopsy, there is interest in developing noninvasive markers of hepatic fibrosis as Noninvasive serum markers, noninvasive diagnostic or imaging tests (e.g., ultrasonography, positron emission tomography, transient elastography and magnetic resonance imaging) and genetic studies for assessing fibrosis have been evaluated (Ray and Thomas, 2009).

This study here is concerned with a specific cytokine of the interleukins family which is interleukin 18 (IL18). It is a novel cytokine inducing the synthesis of IFN-gamma by Th1 cells and has been identified as interferon gamma inducing factor (IGIF) and monitoring its effect in liver cirrhosis. (**Zeng et al., 2007**).