



شبكة المعلومات الجامعية  
التوثيق الإلكتروني والميكرو فيلم

# بسم الله الرحمن الرحيم



**HANAA ALY**



شبكة المعلومات الجامعية  
التوثيق الإلكتروني والميكروفيلم



# شبكة المعلومات الجامعية التوثيق الإلكتروني والميكروفيلم



**HANAA ALY**



شبكة المعلومات الجامعية  
التوثيق الإلكتروني والميكروفيلم

# جامعة عين شمس

## التوثيق الإلكتروني والميكروفيلم

### قسم

نقسم بالله العظيم أن المادة التي تم توثيقها وتسجيلها  
علي هذه الأقراص المدمجة قد أعدت دون أية تغيرات



### يجب أن

تحفظ هذه الأقراص المدمجة بعيدا عن الغبار



**HANAA ALY**



**The use of Neutrophil Gelatinase  
Associated Lipocalin (NGAL) as a novel  
marker in early diagnosis of Hepato Renal  
Syndrome in advanced cirrhotic patients**

Thesis

*Submitted for Partial Fulfillment of Master Degree in  
Internal Medicine & Gastroenterology and Hepatology*

By

**Amr Ahmed Okasha**

*M. B., B.Ch., Faculty of Medicine, Tanta university*

Under supervision of

**Prof. Dr. Nevine Ibrahim Musa**

*Professor of Internal Medicine, Gastroenterology  
Faculty of Medicine - Ain Shams University*

**Dr. Ahmed Samir Abo Halima**

*Assistant Professor of Internal Medicine, Gastroenterology  
Faculty of Medicine - Ain Shams University*

**Dr. Ahmed Samir Allam**

*Lecturer of Internal Medicine, Gastroenterology  
Faculty of Medicine - Ain Shams University*

*Faculty of Medicine  
Ain Shams University*

*2021*



بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

# قَالَ

سَبَّحَانَكَ لَا إِلَهَ إِلَّا مَا عَلَّمْتَنَا إِنَّكَ أَنْتَ  
الْعَلِيمُ الْعَظِيمُ

صدق الله العظيم

سورة البقرة الآية: ٣٢

# Acknowledgment

*First and foremost, I feel always indebted to **ALLAH**,  
the Most Kind and Most Merciful.*

*I'd like to express my respectful thanks and profound gratitude to **Prof. Dr. Nevine Ibrahim Musa**, Professor of Internal Medicine, Gastroentrololgy, Faculty of Medicine - Ain Shams University for his keen guidance, kind supervision, valuable advice and continuous encouragement, which made possible the completion of this work.*

*I am also delighted to express my deepest gratitude and thanks to **Dr. Ahmed Samir Abo Halima**, Assistant Professor of Internal Medicine, Gastroentrololgy, Faculty of Medicine - Ain Shams University, for his kind care, continuous supervision, valuable instructions, constant help and great assistance throughout this work.*

*I am deeply thankful to **Dr. Ahmed Samir Allam**, Lecturer of Internal Medicine, Gastroentrololgy, Faculty of Medicine - Ain Shams University, for his great help, active participation and guidance.*

**Amr Okasha**

# List of Contents

Title	Page No.
List of Abbreviations.....	i
List of Tables .....	ii
List of Figures .....	iv
Introduction .....	1
Aim of the Work.....	6
Review of Literature	
Hepato-Renal Syndrome .....	7
Biomarkers in AKI .....	39
What is NGAL? .....	44
Patients and Methods.....	46
Results .....	53
Discussion .....	83
Summary .....	99
Conclusion .....	105
Recommendations .....	106
References .....	107

# List of Abbreviations

Abb.	Full term
ACLF .....	Acute-on-chronic liver failure
ADQI.....	Acute Dialysis Quality Initiative
AKI .....	Acute kidney injury
AKIN .....	Acute Kidney Injury Network
ATN .....	Acute tubular necrosis
CKD .....	Chronic kidney disease
CRP.....	C-reactive protein
eGFR.....	Estimated glomerular filtration rate
ELISA.....	Enzyme-linked immunosorbent assay
FeNa .....	Fractional excretion of sodium
HRS .....	Hepatorenal syndrome
HRS .....	Hepatorenal syndrome
IAC.....	International Ascites Club
iAKI .....	Intrinsic acute kidney injury
IL .....	Interleukin
KIM-1 .....	Kidney injury molecule-1
L-FABP.....	Liver-type fatty acid-binding protein
LT .....	Liver transplantation
MDRD6.....	Modification of Diet in Renal Disease 6
NGAL .....	Neutrophil gelatinase-associated lipocalin
PRA.....	Prerenal azotemia
RRT.....	Renal replacement therapy
SBP .....	Spontaneous bacterial peritonitis
TIPS.....	Transjugular intrahepatic portosystemic shunting



# List of Tables

Table No.	Title	Page No.
Table (1):	RIFLE classification by ADQI.....	3
Table (2):	AKIN classification.....	4
Table (3):	International Club of Ascites Definition and Staging of AKI in Patients With Cirrhosis.....	9
Table (4):	ICA Diagnostic Criteria of HRS AKI.....	10
Table (5):	Characteristics of Randomized Controlled Trials of Albumin and Vasoconstrictors for Treatment of HRS.....	30
Table (6):	Comparison between different studied groups according to age. ....	54
Table (7):	Comparison between different studied groups according to sex.....	56
Table (8):	Comparison between different studied groups according to CBC.....	57
Table (9):	Comparison between different studied groups according to S.Creat.....	61
Table (10):	Comparison between different studied groups according to S.Urea.....	63
Table (11):	Comparison between different studied groups according to RBG.....	65
Table (12):	Comparison between different studied groups according to INR.....	67
Table (13):	Comparison between different studied groups according to liver enzymes .....	68
Table (14):	Comparison between different studied groups according to S.Albumin. ....	71
Table (15):	Comparison between different studied groups according to Serum Bilirubin.....	72

## List of Tables Cont...

Table No.	Title	Page No.
Table (16):	Comparison between different studied groups according to alfa feto protien .....	73
Table (17):	Comparison between different studied groups according to Sodium level .....	75
Table (18):	Comparison between different studied groups according to Plasma Neutrophil Gelatinase Associated Lipocalin (NGAL) .....	77
Table (19):	Comparison between different studied groups according to Urinary Neutrophil Gelatinase Associated Lipocalin (NGAL) .....	79
Table (20):	Correlation.....	81
Table (21):	Correlation.....	82

# List of Figures

Fig. No.	Title	Page No.
<b>Figure (1):</b>	Stages.....	27
<b>Figure (2):</b>	Comparison between different studied groups according to age.....	55
<b>Figure (3):</b>	Comparison between different studied groups according to Sex .....	56
<b>Figure (4):</b>	Comparison between different studied groups according to CBC.....	58
<b>Figure (5):</b>	Comparison between different studied groups according to S.Creat .....	61
<b>Figure (6):</b>	Comparison between different studied groups according to S.Urea .....	63
<b>Figure (7):</b>	Comparison between different studied groups according to RBG .....	65
<b>Figure (8):</b>	Comparison between different studied groups according to INR .....	67
<b>Figure (9):</b>	Comparison between different studied groups according to liver enzymes.....	69
<b>Figure (10):</b>	Comparison between different studied groups according to S.Albumin .....	71
<b>Figure (11):</b>	Comparison between different studied groups according to serum bilirubin. ....	72
<b>Figure (12):</b>	Comparison between different studied groups according to Alfa feto protein.....	73
<b>Figure (13):</b>	Comparison between different studied groups according to sodium level.....	75
<b>Figure (14):</b>	Comparison between different studied groups according to Plasma Neutrophil Gelatinase Associated Lipocalin (NGAL).....	77
<b>Figure (15):</b>	Comparison between different studied groups according to Urinary Neutrophil Gelatinase Associated Lipocalin (NGAL).....	79

# INTRODUCTION

Kidney dysfunction is a complex and common event in patients with liver cirrhosis. Although novel treatments have shown some promising results (*Kaushal and Shah, 2014*), acute kidney injury (AKI) remains a major complication of decompensated liver cirrhosis with high morbidity and mortality rates (*Garcia-Tsao et al., 2008; Siew et al., 2009*). AKI occurs in up to 19-20% of hospitalized patients with liver cirrhosis and among the most frequent causes are prerenal azotemia (PRA), hepatorenal syndrome (HRS), and acute tubular necrosis (ATN), with prevalence rates estimated around 68%, 25%, and 33%, respectively (*Garcia-Tsao et al., 2008; Siew et al., 2009*). Reports have shown that approximately 1% of cirrhotic patients with azotemia suffer from progressive parenchymal renal disease secondary to hepatic viral infections, immune or metabolic disorders (chronic glomerulonephritis, IgA nephropathy, diabetic nephropathy) (*Garcia-Tsao et al., 2008; Hartleb and Gutkowski, 2012*).

## Definitions of AKI and CKD

In 2011, after a joint debate, members of the Acute Dialysis Quality Initiative (ADQI) and the International Ascites Club (IAC) developed a new collection of diagnostic criteria for an improved evaluation of kidney impairment in liver cirrhosis (*Wong et al., 2011; Choi et al., 2014*). The term “Acute Kidney Injury (AKI)” is used to describe the abrupt

decline of the renal function indicated by a boost in serum creatinine level of  $>50\%$  from baseline, or by an upward trend in serum creatinine level of  $\geq 26.4 \mu\text{mol/L}$  ( $\geq 0.3 \text{ mg/dL}$ ) in less than 48 hours. Chronic Kidney Disease (CKD) can be defined by an estimated glomerular filtration rate (eGFR) below 60 ml/minute for more than 3 months, by using the Modification of Diet in Renal Disease 6 (MDRD6) formula. Acute chronic kidney disease manifests as an overlapping of AKI on pre-existing chronic renal disease according to the previous definitions for AKI and CKD (*Wong et al., 2011; Choi et al., 2014*).

## **RIFLE classification**

Gathered together in Vicenza (Italy) in May 2002, the members of ADQI group elaborated a new set of diagnostic and classification criteria for AKI: the RIFLE classification (published in May 2004). This classification system includes three classes for severity (Risk, Injury, Failure) and another two classes for outcome (Loss of kidney function, End-stage kidney disease) defined by perturbations in serum creatinine, glomerular filtration rate or urine output as described in Table 1 (*Lopes and Jorge, 2013*).

**Table (1):** RIFLE classification by ADQI (*Bellomo et al., 2004; Lopes and Jorge, 2013; Choi et al., 2014*).

Class	GFR criteria	UO criteria	
<b>Risk</b>	$\uparrow \text{SCr} \times 1.5$ or $\downarrow \text{GFR} > 25\%$	$< 0.5 \text{ mL/kg/h} \times 6 \text{ h}$	Severity classes
<b>Injury</b>	$\uparrow \text{SCr} \times 2$ or $\downarrow \text{GFR} > 50\%$	$< 0.5 \text{ mL/kg/h} \times 12 \text{ h}$	
<b>Failure</b>	$\uparrow \text{SCr} \times 3$ or $\downarrow \text{GFR} > 75\%$ or if baseline $\text{SCr} \geq 353.6 \mu\text{mol/L}$ ( $\geq 4 \text{ mg/dL}$ ) $\uparrow \text{SCr} > 44.2 \mu\text{mol/L}$ ( $> 0.5 \text{ mg/dL}$ )	$< 0.3 \text{ mL/kg/h} \times 24 \text{ h}$ or anuria $\times 12 \text{ h}$	
<b>Loss of kidney function</b>	Complete loss of kidney function $> 4$ weeks		Outcome classes
<b>End-stage kidney disease</b>	Complete loss of kidney function $> 3$ months		
GFR = glomerular filtration rate; UO = urine output; SCr = serum creatinine			

## AKIN classification

After a meeting in Amsterdam (September 2005), the Acute Kidney Injury Network (AKIN) group developed a new set of criteria for AKI known as the AKIN classification (published in March 2007). This improved the classification system which consisted of 3 stages of severity and was based only on changes in serum creatinine (2 measurements within 48 h) and urine output as shown in **Table 2** (*Lopes and Jorge, 2013*).



**Table (2):** AKIN classification (*Lopes and Jorge, 2013; Choi et al., 2014*).

Stage	SCr criteria	UO criteria
<b>1</b>	↑ SCr $\geq 26.5 \mu\text{mol/L}$ ( $\geq 0.3 \text{ mg/dL}$ ) or ↑SCr $\geq 150\text{-}200\%$ ( $1.5\text{-}2\times$ )	$<0.5 \text{ mL/kg/h}$ ( $>6 \text{ h}$ )
<b>2</b>	↑ SCr $>200\text{-}300\%$ ( $>2\text{-}3\times$ )	$<0.5 \text{ mL/kg/h}$ ( $>12 \text{ h}$ )
<b>3</b>	↑ SCr $>300\%$ ( $>3\times$ ) or if baseline SCr $\geq 353.6 \mu\text{mol/L}$ ( $\geq 4 \text{ mg/dL}$ ) an ↑SCr $\geq 44.2 \mu\text{mol/L}$ ( $\geq 0.5 \text{ mg/dL}$ )	$<0.3 \text{ mL/kg/h}$ ( $>24 \text{ h}$ ) or anuria ( $>12 \text{ h}$ )
SCr = serum creatinine; UO = urine output. * patients requiring RRT are included independent of the stage		

A common limitation of both classifications systems is their inability to provide any information on the cause of the renal dysfunction in liver cirrhosis. Existing data cannot support the superiority of AKIN classification to traditional criteria regarding risk prediction in patients with liver cirrhosis and renal failure (*Arroyo, 2013*). Fagundes et al. observed that a combination between AKIN classification and traditional criteria for kidney impairment might provide a better assessment of risk in patients with liver cirrhosis, compared with AKIN criteria alone (*Fagundes et al., 2013*).