# The Role of Renovascular Duplex and Serum Cystatin C in the Prediction of Hepatorenal Syndrome in Critically Ill Liver Cirrhotic Patients

*Thesis*

Submitted For Partial Fulfillment of MD Degree in

**CRITICAL CARE MEDICINE**

*Investigator*

**Ibrahim Mohamed Abdel Azim**

**M.B., B.Ch., M.Sc.**

*Supervisors*

**Dr. WaheedRadwan, MD**

Prof. of Critical Care Medicine
Critical Care Department,
Cairo University

**Dr. Mervat El-Damarawy, MD**

Prof. of Internal Medicine
Head of Department of Critical Care Medicine
Theodor Bilharz Research Institute

**Dr. Osama Tayeh, MD**

Assist. Prof. of Critical Care Medicine
Critical Care Department,
Cairo University

**Dr. HazemHossam, MD**

Lecturer of Critical Care Medicine
Critical Care Department,
Cairo University

**Cairo University**

**2014**

# دور دوبلكس الاوعية الدموية الكلوية و مستوى السيستاتين سي بالدم في التنبؤ بالمتلازمة الكبدية الكلوية في مرضى التليف الكبدي ذوي الحالات الحرجة


رسالةمقدمة من الطبيب

إبراهيم محمد عبد العظيم


توطئة للحصول على درجة الدكتوراه
فى طب الحالات الحرجة

تحت إشراف


**أ.د. وحيد أحمد رضوان**
أستاذ طب الحالات الحرجة
جامعة القاهرة

**أ.د. ميرفت الدمراوى**
أستاذ الباطنة العامة
رئيس قسم العناية المركزة
معهد تيودور بلهارس للأبحاث

**د. أسامة طايع**
أستاذ م. طب الحالات الحرجة
جامعة القاهرة

**د. حازم حسام الدين عبد الحق**
مدرس طب الحالات الحرجة
جامعة القاهرة



جامعة القاهرة
2014

بسم الله الرحمن الرحيم

(قَالُوا سُبْحَانَكَ لا عِلْمَ لَنَا
إِلَّا مَا عَلَّمْتَنَا إِنَّكَ أَنْتَ
الْعَلِيمُ الْحَكِيمُ)

صدق الله العظيم

(سورة البقرة:32)

جامعة القاهرة / كلية الطب
الدراسات العليا

محضر
اجتماع لجنة الحكم على الرسالة المقدمة من
الطبيب /
توطئة للحصول على درجة الماجستير / الدكتوراه
في

تحت عنوان : باللغة الانجليزية : The role of Renovascular duplex and Serum Cystatin C in the Prediction of Hepatorenal Syndrome In Critically ill Liver Cirrhotic Patients

باللغة العربية : دور دوبلكس الأوعية الكلوية والمصل السيستاتين سي في التنبؤ بمتلازمة الكبد الكلوية في مرضى تليف الكبد الحرجة

بناء على موافقة الجامعة بتاريخ ٢ / ٢ / ٢٠١٤ تم تشكيل لجنة الفحص والمناقشة للرسالة المذكورة أعلاه على النحو التالي :-

١. أ.د. وحيد أحمد سواحل ..... من المشرفين
٢. أ.د. كامل عبد العزيز محمد ..... ممتحن داخلي
٣. أ.د. [illegible] ..... ممتحن خارجي

بعد فحص الرسالة بواسطة كل عضو منفردا وكتابة تقارير منفردة لكل منهم انعقدت اللجنة مجتمعة في يوم الاثنين بتاريخ ٢١ / ٧ / ٢٠١٤ بقسم طب الحالات الحرجة مدرج الوحدة الثاني بكلية الطب – جامعة القاهرة وذلك لمناقشة الطالب في جلسة علنية في موضوع الرسالة والنتائج التي توصل اليها وكذلك الأسس العلمية التي قام عليها البحث .

قرار اللجنة :

تم قبول الرسالة شكلا وموضوعا

توقيعات أعضاء اللجنة :-

| المشرف الممتحن | الممتحن الداخلي | الممتحن الخارجي |
| --- | --- | --- |
| ..... | ..... | ..... |

عصام

# Acknowledgement

*Thanks and for most thanks to* ***ALLAH,*** *the merciful of all, who helped me for accomplishement of this work.*

*I am extremely grateful to* ***Professor Dr. Waheed Ahmed Radwan****, Professor of Critical Care Medicine, Faculty of Medicine Cairo University,for his sincere co-operation, continuous unlimited help, also his accurate supervision through every step taken in this work and the most fruitful pieces of advice and continuous guidance during execution of this work .*

*My deep gratitude goes to* ***Professor Dr. Mervat Mohammed El Damarawy****, Professor of Internal Medicine Head of Department of Critical Care Medicine Theodor Bilharz Research Institutefor her endless support,valuable assistance without which I would not have done nothing valuable through her continuous supervision in all the details of this work and helpful suggestions and continuousencouragement.*

*I wish to extend my gratitude and deepest appreciation to* ***Professor Dr.*** ***Osama Mohamed Tayeh****,Assistant Professor of Critical Care Medicine, Faculty of Medicine , Cairo University for his helpful supervision in conducting this study through his great contribution through accomplishment of the clinical part of the study which brought our work to light, also for endless creativity and helpful supervision that have always stimulated me to spare no effort to get this study born to life and can never forget to mention the great support and help by* ***Dr.Hazem Hossam El Din Abd El Haq, MD*** *Lecturer of Critical Care Medicine, Faculty of Medicine ,Cairo University*

*Lastly but not least, I feel deeply thankful to my dear family for their continuous support.*

*Ibrahim Mohamed Abdel Azim.*

# Dedication

***My work is dedicated to:***

*My Great Good Allah,*
*Merciful, Al-Aliem,*
*Al-Khabeer*
*&*
*My beloved Prophet Mohammed*
*Peace and Blessings of ALLAH*
*upon him*

***Whose efforts and guidance made me able to serve this noble profession of medical science.***

# Abstract


- Background: Hepatorenal syndrome (HRS) is a “functional” and reversible form of renal failure that occurs in patients with advanced chronic liver disease. Doppler ultrasonography is a non-invasive tool for the assessment of vascular patency and has been used to measure hepatic arterial and venous flow in patients with portal hypertension. Several studies have reported that the reciprocal of cystatin C correlates better with GFR than does the reciprocal of creatinine. Methods: 40 patients, of whom 10 persons were normal volunteers taken as a control group, Group A patients (No. =20) with liver cirrhosis and normal renal functions had been followed up for an average of 12 months searching for development of hepatorenal syndrome HRS. Results &conclusions: During the follow up, 5 patients developed HRS, serum cystatin level showed a more statistically significant rise in the same patients with higher P value. Using ROC curves support an advantage of cystatin C over serum creatinine. Using multiple variables in cox regression model, we found that the risk of death is higher if increasing cystatin c with highly significant value (P value 0.001). When used ROC curves for R.I. RI at a level of 0.66 showed 80% sensitivity and 90%specificity.



**Key Words:** (hepatorenal syndrome; serum cystatin C; renal resistivity index**)**

# Contents

# List of Tables

# List of Figures

# List of abbreviation

| | | |
|---|---|---|
| **ADQI** | : | Acute Dialysis Quality Initiative |
| **ATN** | : | Acute Tubular Necrosis |
| **AST** | : | Aspartate Aminotransferase |
| **ALT** | : | Alanine Aminotransferase |
| **ALP** | : | Alkaline Phosphatase |
| **AIDS** | : | Acquired Immune Deficiency Syndrome |
| **ARF** | : | Acute Renal Failure |
| **AUC** | : | Area Under The Curve |
| **BP** | : | Blood Pressure |
| **CBF** | : | Central Blood Flow |
| **CKD** | : | Chronic Kidney Disease |
| **CPT** | : | Child Pugh Turcotte |
| **CNS** | : | Central Nervous System |
| **CO** | : | Cardiac Output |
| **CrCl** | : | Creatinine Clearance |
| **CysC** | : | Cystatin C |
| **CT** | : | Computerized Tomography |
| **DM** | : | Diabetes Mellitus |
| **DNA** | : | Deoxyribonucleic Acid |
| **DD** | : | Differential Diagnosis |
| **ESLD** | : | End-Stage Liver Disease |
| **EDTA** | : | Ethylenediaminetetraacetic Acid |
| **FDA** | : | Food And Drug Administration |
| **GGT** | : | Gamma GlutamylTranspeptidase |
| **GFR** | : | Glomerular Filteration Rate |
| **HD** | : | Hemodialysis |
| **HIV** | : | Human Immunodeficiency Virus |
| **HRS** | : | Hepatorenal Syndrome |
| **HBV** | : | Hepatitis B Virus |
| **HCV** | : | Hepatitis C Virus |

| | | |
|---|---|---|
| **H/O** | : | History |
| **HSC** | : | Hepatic Stellate Cells |
| **HCC** | : | Hepatocellular Carcinoma |
| **HTN** | : | Hypertension |
| **IAC** | : | Intersocietal Accreditation Commision |
| **IL** | : | Interleukin |
| **INR** | : | International Normalized Ratio |
| **Ig** | : | Immunoglobulin |
| **K** | : | Potassium |
| **kDa** | : | Kilodalton |
| **Kt/V** | : | Clearance Time / Volume |
| **KIM** | : | Kidney Injury Molecule |
| **LFT** | : | Liver Function Test |
| **L.C** | : | Liver Cirrhosis |
| **MDRD** | : | Modification Of Diet In Renal Disease |
| **MRI** | : | Magnetic Resonance Imaging |
| **m** | : | Month |
| **Mg/dl** | : | Milligram Per Deciliter |
| **mEq** | : | Milliequvalent |
| **mL** | : | Milliliter |
| **mmol** | : | Millimole |
| **MELD** | : | Model For End Stage Liver Disease |
| **NASH** | : | Nonalcoholic Steatohepatitis |
| **NAFLD** | : | Nonalcoholic Fatty Liver Disease |
| **NIDDM** | : | Non-Insulin Dependent Diabetes Mellitus |
| **S or u NGAL** | : | Neutrophil Gelatinase-Associated Lipocalin (Serum Or Urinary) |
| **N.** | : | Number |
| **Na** | : | Sodium |
| **NO** | : | Nitric Oxide |
| **NSAID** | : | Non-Steroidal Anti- Inflammatory Drugs |
| **OLT** | : | Orthotopic Liver Transplantation |
| **P** | | P Value |
| **PD** | | Peritoneal Dialysis |

| | |
|---|---|
| **PI** | Pulsatility Index |
| **P.H** | Portal Hypertension |
| **Pt** | Patient |
| **PT** | Prothrombin Time |
| **PTT** | Partial Thromboplastin Time |
| **RA** | Renal Artery |
| **RAA** | Renin Angiotensin Aldosterone |
| **RBF** | Renal Blood Flow |
| **ROC** | Receiver Operating Characteristic |
| **RNA** | Ribonucleic Acid |
| **REFs** | References |
| **RI** | Resistivity Index |
| **RRF** | Residual Renal Function |
| **RRT** | Renal Replacement Therapy |
| **RIA** | Radioimmunoassay |
| **SCr** | Serum Creatinine |
| **SD** | Standard Deviation |
| **SBP** | Spontaneous Bacterial Peritonitis |
| **SNS** | Sympathetic Nervous System |
| **SPSS** | Statistical Package For Scientific Studies |
| **TIPS** | Transjugular Intrahepatic Portocaval Shunt |
| **TLC** | Total Leucocytic Count |
| **T.Bil** | Total Bilirubin |
| **TNF** | Tumour Necrosis Factor |
| **Tc-DPTA** | Technetium - Diethylene-Triamine-Pentaacetate |
| **US** | Ultrasonogram |
| **UNOS** | United Network Of Organ Sharing |
| **VD** | Vasodilator |
| **VC** | Vasoconstrictor |
| **WHO** | World Health Organization |
| **yr** | Year |
| **µL** | Microlitre |

# Chapter I

## Liver Cirrhosis

### ➢ Introduction:

Liver cirrhosis is the final stage of various chronic liver diseases. The concept is essentially morphological, defined as a diffuse alteration of hepatic architecture by the presence of necrosis, fibrosis and regenerative nodules. These disorders conduct to intrahepatic vascular changes and to the reduction of functional mass. Finally, the consequences are the development of portal hypertension and the occurrence of liver failure ***(Ampurdanéset al., 2002).***

### ➢ Natural history of liver cirrhosis and its complications:

The studies that provide more data on the natural history of cirrhosis are related to the evolution of chronic hepatitis by HBV and HCV. These are based on prospective, retrospective and cross studies, but are conditioned by factors that make difficult to establish absolute evidence on the natural history of the disease***(Serra et al., 2006)***.

Of those patients with HCV, 50% usually develop chronic liver disease including cirrhosis and liver cancer. It is estimated that 15% of chronically infected persons develop liver cirrhosis within 20 years ***(Wiese et al., 2005).***

However, there are individual differences. Currently it is known that 33% of patients develop cirrhosis in less than 20 years, while another 31% will need many more years in order to develop the same damage ***(Serra et al., 2006).***

Usually it is a silent disease. Most patients are asymptomatic or have nonspecific symptoms until decompensation occurs. They can start with symptoms related to complications of liver failure or portal hypertension. Ascites is the most common complication and of earlier onset. Once patients with cirrhosis develop ascites the prognosis worsens ***(Sagnelliet al.,2005).***It is estimated that approximately 50% of them could die within two years if they do not have a transplant ***(Sagnelliet al., 2005).***

Along with ascites, there may be other serious complications such as spontaneous bacterial peritonitis. In these cases, the probability of survival one year after this complication appears is only 40%. This is a strong reason for evaluating these patients as candidates for transplantation ***(Corraoet al., 1997)***.

Similarly, other complications may appear such as hepaticencephalopathy and hepatorenal syndrome. Both also worsen the prognosis. ***(Mendez-Sanchez et al., 2005).***

Variceal hemorrhage occurs in 30 to 40% of patients with liver cirrhosis. In the past two decades, even with the improvement achieved in the treatment and in the prognosis after bleeding, mortality at six weeks is