



شبكة المعلومات الجامعية  
التوثيق الإلكتروني والميكروفيلم

# 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**



# **Screening of Cirrhotic Compensated Hepatitis C Virus Infected Patients who Received Oral Direct Acting Antiviral Drugs for Hepatocellular Carcinoma and Other Malignancies**

*Thesis*

*Submitted for Fulfillment of MD Degree in  
Internal Medicine*

*Presented by*  
**Ahmed Mahmoud Sabry Emam**  
*M.Sc*

*Under Supervision of*  
**Prof. Dr. Osama Aboelfotoh El Sayed Aly**  
*Professor of Internal Medicine and Gastroenterology  
Faculty of Medicine - Ain-Shams University*

**Prof. Dr. Enas Mahmoud Fouda**  
*Professor of Internal Medicine and Gastroenterology  
Faculty of Medicine - Ain-Shams University*

**Prof. Dr. Magdy Galal Eldin Abdelrahman**  
*Professor of Internal Medicine and Gastroenterology  
Faculty of Medicine - Ain-Shams University*

**Prof. Dr. Ashraf Aboubakr**  
*Professor of Internal Medicine and Gastroenterology  
Military Medical Academy*

*Faculty of Medicine  
Ain-Shams University*

*2021*



بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قَالَ

سَبِّحْ اِنَّكَ لَا تَعْلَمُ لَنَا  
اِلَّا مَا عَلَّمْتَنَا اِنَّكَ اَنْتَ  
الْعَلِيمُ الْعَظِيمُ

صدق الله العظيم

سورة البقرة الآية: ٣٢

بسم الله الرحمن الرحيم

وأنزل الله عليك الكتاب

والحكمة وعلمك ما لم تكن تعلم

وكان فضل الله عليك عظيما

صدق الله العظيم

سورة النساء

آية (١١٢)

# Acknowledgment

*First of all, I wish to express my sincere thanks to **ALLAH** for his care and generosity throughout my life.*

*I would like to express my sincere appreciation and my deep gratitude to **Prof. Dr. Osama Abo El-Fotoh El Sayed Aly**, Professor of Internal Medicine and Gastroenterology, Ain-Shams University for his faithful supervision and guidance.*

*I am also deeply indebted to **Prof. Dr. Enas Mahmoud Fouda**, Professor of Internal Medicine and Gastroenterology, Ain Shams University for his great support throughout the whole work.*

*I would like to express my great thanks to **Prof. Dr. Magdy Galal Eldin Abdelrahman**, Professor of Internal Medicine and Gastroenterology, Ain Shams University for the tremendous effort he has done in the meticulous revision of this work.*

*At last, I would like to express my appreciation and great thanks to my leader **Prof. Dr. Ashraf Ahmed Abu Bakr** Consultant of Internal Medicine and Gastroenterology, Military Medical Academy for his great effort and support all the time ao the study.*

*Ahmed Sabry*

## *Dedication*

*To:*

*The soul of my mother*

*To my father*

*Who gave me too much  
And received too little,*

*My wife and my lovely  
children*



# *List of Contents*

| Title                                   | Page No. |
|-----------------------------------------|----------|
| List of Abbreviations.....              | i        |
| List of Tables .....                    | iv       |
| List of Figures .....                   | vi       |
| Introduction .....                      | 1        |
| Aim of the Work.....                    | 4        |
| Review of Literature                    |          |
| Hepatitis C Virus.....                  | 5        |
| Hepatocellular Carcinoma (HCC).....     | 20       |
| Oral Direct Acting Antiviral Drugs..... | 76       |
| Patients and Methods.....               | 93       |
| Results .....                           | 99       |
| Discussion .....                        | 132      |
| Summary .....                           | 143      |
| Conclusion.....                         | 146      |
| Recommendations .....                   | 148      |
| References .....                        | 149      |
| Arabic Summary .....                    | —        |

# *List of Abbreviations*

| Abb.                  | Full term                                           |
|-----------------------|-----------------------------------------------------|
| <b>AASLD</b> .....    | American association for the study of liver disease |
| <b>ACR</b> .....      | Acute Cellular Rejection                            |
| <b>AFP</b> .....      | Alpha fetoprotein                                   |
| <b>ALT</b> .....      | Alanine amino transferase                           |
| <b>AST</b> .....      | Aspartate amino trasnaminase                        |
| <b>ASV</b> .....      | Asunaprevir                                         |
| <b>ATG</b> .....      | Antithymoglobulin                                   |
| <b>BMD</b> .....      | Bone mineral density                                |
| <b>BOC</b> .....      | Boceprevir                                          |
| <b>CAD</b> .....      | Coronary artery disease                             |
| <b>CIT</b> .....      | Cold Ischemia Time                                  |
| <b>CLD</b> .....      | Chronic Liver Disease                               |
| <b>CMV</b> .....      | Cytomegallo virus                                   |
| <b>CNIs</b> .....     | Calcineurin Inhibitors                              |
| <b>CT</b> .....       | Computed Tomograghy                                 |
| <b>CTP</b> .....      | Child-Turcotte-Pugh Score                           |
| <b>CYP- 3A4</b> ..... | Cytochrome P 3A4                                    |
| <b>CYP 450</b> .....  | Cytochrome P 450                                    |
| <b>DAAs</b> .....     | Direct Acting Antivirals                            |
| <b>DCV</b> .....      | Daclatasvir                                         |
| <b>DDLT</b> .....     | Deceased Donor Liver Trensplantation                |
| <b>EBV</b> .....      | Epstein Bar Virus                                   |
| <b>EDHS</b> .....     | Egypt Demographic and Health Survey                 |
| <b>ELTR</b> .....     | European Liver Transplant Rigestry                  |
| <b>ESLD</b> .....     | End Stage Liver Disease                             |
| <b>GAG</b> .....      | Glycosaminoglycan                                   |
| <b>GFR</b> .....      | Glomerular filtration rate                          |
| <b>GRWR</b> .....     | Graft recipient weight ratio                        |

## *List of Abbreviations Cont...*

| Abb.                 | Full term                                                   |
|----------------------|-------------------------------------------------------------|
| <b>HALT-C .....</b>  | Hepatitis C antiviral long term treatment against cirrhosis |
| <b>HBIG.....</b>     | Hepatitis B immunoglobulin                                  |
| <b>HBV.....</b>      | Hepatitis B Virus                                           |
| <b>HCC .....</b>     | Hepatocellular Carcinoma                                    |
| <b>HCV.....</b>      | Hepatitis C Virus                                           |
| <b>HFL.....</b>      | Hepatic focal lesion                                        |
| <b>HIV.....</b>      | Human immunodeficiency virus                                |
| <b>HLA.....</b>      | Human leucocyte antigen                                     |
| <b>HPS.....</b>      | Hepatopulmonary Syndrome                                    |
| <b>IL2.....</b>      | Interlukein 2                                               |
| <b>INR.....</b>      | International normalized ratio                              |
| <b>IRES.....</b>     | Internal Ribosomal Entry Site                               |
| <b>LDL .....</b>     | Low Density Lipoprotein                                     |
| <b>LDLT .....</b>    | Living Donor Liver Transplantation                          |
| <b>LTs .....</b>     | Liver Transplantation                                       |
| <b>MELD .....</b>    | Model for end stage liver disease                           |
| <b>MHC.....</b>      | Major histocompatibility complex                            |
| <b>MMF.....</b>      | Mycophenol Mofetil                                          |
| <b>NI.....</b>       | Nucleoside inhibitors                                       |
| <b>NODM.....</b>     | New onset diabetes mellitus                                 |
| <b>NTR.....</b>      | Non Translated Region                                       |
| <b>ORF.....</b>      | Open Reading Frame                                          |
| <b>PBC .....</b>     | Primary biliary cirrhosis                                   |
| <b>PCR.....</b>      | Polymerase Chain Reaction                                   |
| <b>PEG-INF .....</b> | Pegylated Interferone                                       |
| <b>PELD .....</b>    | Pediatric End Stage Liver Disease                           |
| <b>PIs .....</b>     | Protease inhibitors                                         |
| <b>PPV .....</b>     | Positive Predective value                                   |

## *List of Abbreviations Cont...*

| Abb.              | Full term                                         |
|-------------------|---------------------------------------------------|
| <b>PSC</b> .....  | Primary Sclerosing Cholangitis                    |
| <b>PTLD</b> ..... | Post transplant lymphoproliferative disease       |
| <b>RBV</b> .....  | Ribavirin                                         |
| <b>RdRp</b> ..... | RNA dependant RNA polymerase                      |
| <b>SD</b> .....   | Standard deviation                                |
| <b>SOC</b> .....  | Standard of care                                  |
| <b>SOF</b> .....  | Sofosbuvir                                        |
| <b>SP</b> .....   | Signal Peptidase                                  |
| <b>SPP</b> .....  | Signal Peptide Peptidase                          |
| <b>SVR</b> .....  | Sustained Virological Response                    |
| <b>TIPS</b> ..... | Transjugular intrahepatic portosystemic<br>shunts |
| <b>TPV</b> .....  | Telaprevir                                        |
| <b>UNOS</b> ..... | United Network For organ Sharing                  |
| <b>US</b> .....   | Ultrasound                                        |
| <b>UTR</b> .....  | Untranslated Region                               |

# *List of Tables*

| Table No.          | Title                                                                                                                                            | Page No. |
|--------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|----------|
| <b>Table (1):</b>  | HCC risk development factors (%).....                                                                                                            | 25       |
| <b>Table (2):</b>  | Recommendations for HCC surveillance;<br>Categories of adult patients in whom<br>surveillance is recommended .....                               | 44       |
| <b>Table (3):</b>  | The Eastern Cooperative Oncology<br>Group performance status .....                                                                               | 50       |
| <b>Table (4):</b>  | Several tumor markers and their clinical<br>uses .....                                                                                           | 52       |
| <b>Table (5):</b>  | Causes of elevated alpha fetoprotein .....                                                                                                       | 54       |
| <b>Table (6):</b>  | Summary of treatment recommendations<br>according to the genotype .....                                                                          | 87       |
| <b>Table (7):</b>  | Socio-demographic and clinical data<br>among cases and controls.....                                                                             | 99       |
| <b>Table (8):</b>  | Baseline laboratory data among cases<br>and controls:.....                                                                                       | 101      |
| <b>Table (9):</b>  | Baseline Fibroscan assessment for cases<br>and controls.....                                                                                     | 102      |
| <b>Table (10):</b> | Baseline ultrasound assessment.....                                                                                                              | 102      |
| <b>Table (11):</b> | Comparison between the 4 groups as<br>regards socio-demographic and clinical<br>data using Kruskal-Wallis and Chi<br>square tests:.....          | 104      |
| <b>Table (12):</b> | Comparison between the 4 groups as<br>regards (baseline) laboratory and<br>radiological data using Kruskal-Wallis<br>and Chi square tests: ..... | 105      |



## *List of Tables Cont...*

| Table No.          | Title                                                                                                                                           | Page No. |
|--------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|----------|
| <b>Table (13):</b> | Comparison between A group of patients as regards serial laboratory and radiological measurements:.....                                         | 110      |
| <b>Table (14):</b> | Comparison between B group of patients as regards serial laboratory and radiological measurements:.....                                         | 112      |
| <b>Table (15):</b> | Comparison between C group of patients as regards serial laboratory and radiological measurements:.....                                         | 114      |
| <b>Table (16):</b> | Comparison between D group of patients as regards serial laboratory and radiological measurements:.....                                         | 116      |
| <b>Table (17):</b> | Comparison between the 4 groups of patients as regards serial laboratory measurements using repeated measures ANOVA test (4-Factor study):..... | 118      |
| <b>Table (18):</b> | Comparison between the 4 groups as regards final HCC diagnosis using Kruskal-Wallis and Chi square tests:.....                                  | 124      |
| <b>Table (19):</b> | Logistic regression model for the Factors affecting HCC occurrence using Forward method:.....                                                   | 127      |
| <b>Table (20):</b> | Roc-curve of some baseline laboratory Factors to predict patients with HCC (32) from patients without (208): .....                              | 128      |
| <b>Table (21):</b> | Roc-curve of some drug combinations to predict patients with HCC (32) from patients without (208): .....                                        | 129      |
| <b>Table (22):</b> | Mean survival time of each group:.....                                                                                                          | 131      |

# *List of Figures*

| Fig. No.            | Title                                                                                                                                                                                           | Page No. |
|---------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|
| <b>Figure (1):</b>  | Hepatitis C virus prevalence among adults and genotype distribution in Asia, Australia and Egypt .....                                                                                          | 6        |
| <b>Figure (2):</b>  | A schematic representation of hepatitis C viral genome .....                                                                                                                                    | 9        |
| <b>Figure (3):</b>  | Model of the HCV life cycle.....                                                                                                                                                                | 12       |
| <b>Figure (4):</b>  | Incidence and mortality of HCC in Egyptian men.....                                                                                                                                             | 22       |
| <b>Figure (5):</b>  | Incidence and mortality of HCC in Egyptian women.....                                                                                                                                           | 23       |
| <b>Figure (6):</b>  | Diagnostic algorithm and recall policy.....                                                                                                                                                     | 48       |
| <b>Figure (7):</b>  | The updated BCLC staging system for HCC.....                                                                                                                                                    | 49       |
| <b>Figure (8):</b>  | Well-differentiated HCC, in cell block preparations .....                                                                                                                                       | 67       |
| <b>Figure (9):</b>  | Moderately differentiated HCC, showing malignant hepatocytes with abundant eosinophilic granularcytoplasm, coarse granular chromatin, prominent nucleoli, and sinusoidal endothelial cells..... | 68       |
| <b>Figure (10):</b> | Poorly differentiated HCC, showing pleomorphic tumor giant cells with bizarre nuclei.....                                                                                                       | 68       |
| <b>Figure (11):</b> | Gender distribution. ....                                                                                                                                                                       | 100      |
| <b>Figure (12):</b> | Comparison between the 4 groups as regards Hb. ....                                                                                                                                             | 107      |
| <b>Figure (13):</b> | Comparison between the 4 groups as regards TLC. ....                                                                                                                                            | 107      |
| <b>Figure (14):</b> | Comparison between the 4 groups as regards creatinine. ....                                                                                                                                     | 108      |