

شبكة المعلومات الجامعية التوثيق الإلكتروني والميكروفيلو

بسم الله الرحمن الرحيم





MONA MAGHRABY



شبكة المعلومات الجامعية التوثيق الإلكتروني والميكروفيلو



شبكة المعلومات الجامعية التوثيق الالكتروني والميكروفيلم



MONA MAGHRABY



شبكة المعلومات الجامعية التوثيق الإلكترونى 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



MONA MAGHRABY

Incidence of Hepatocellular Carcinoma in Hepatitis C patients treated with Direct-Acting Antivirals and Its Relation to Hepatic Fibrosis Stage

Thesis

Submitted for Partial Fulfilment of the M.D Degree in Internal Medicine

Bv

Mazen Moussa Elsheikh M.B.B.CH, M.sc Under Supervision of

Prof. Dr. Maha Ahmed ElTouny

Professor of Internal Medicine and Gastroenterology
Faculty of Medicine - Ain-Shams University

Prof. Dr. Amal Shawky Bakir

Professor of Internal Medicine and Gastroenterology Faculty of Medicine - Ain-Shams University

Dr. Mostafa Shaaban Ahmed

Assistant Professor of Internal Medicine and Gastroenterology
Military Medical Academy

Dr. Ayman Gamil Anwar

Lecturer of Internal Medicine and Gastroenterology Faculty of Medicine - Ain-Shams University

Dr. Yasser Omar Abdelrahman

Lecturer of Internal Medicine and Gastroenterology
Faculty of Medicine - Ain-Shams University
Faculty of Medicine
Ain Shams University
2021



First, thanks are all due to **Allah** for Blessing this work until it has reached its end, as a part of his generous help throughout our life.

My profound thanks and deep appreciation to **Prof. Dr.**Maha Ahmed ElTouny, Professor of Internal Medicine and Gastroenterology, Faculty of Medicine - Ain-Shams University, for her great support and advice, her valuable remarks that gave me the confidence and encouragement to fulfill this work.

I am deeply grateful to **Prof. Dr. Amal Shawky Bakir,** Professor of Internal Medicine and Gastroenterology, Faculty of Medicine - Ain-Shams University, for adding a lot to this work by her experience and for her keen supervision.

I am also thankful to Ass. Prof. Dr. Mostafa Shaaban
Ahmed, Assistant Professor of Internal Medicine and
Gastroenterology, Military Medical Academy, for his valuable
supervision, co-operation and direction that extended throughout
this work.

I would like to direct my special thanks to **Dr. Ayman Gamil Anwar**, Lecturer of Internal Medicine and

Gastroenterology, Faculty of Medicine - Ain-Shams University,
for his valuable help, fruitful advice, continuous support offered
to me and guidance step by step till this essay finished.

I cannot forget the great help of **Dr. Yasser Omar**Abdelrahman, Lecturer of Internal Medicine and

Gastroenterology, Faculty of Medicine - Ain-Shams University, for his valuable efforts, tireless guidance and for his patience and support to get this work into light.

I am extremely sincere to my family who stood beside me throughout this work giving me their support.

Words fail to express my love, respect and appreciation to my wife for her unlimited help and support.



Mazen Moussa Elsheikh

List of Contents

| | Page |
|--|-----------|
| Acknowledgment | |
| List of Abbreviations | ii |
| List of Figures | v |
| List of Tables | vii |
| Introduction | 1 |
| Aim of The Work | 3 |
| Review of Literature | 4 |
| Chapter 1: Hepatitis C Virus | 4 |
| Chapter 2: Treatment of HCV Infection | 22 |
| Chapter 3: Hepatocellular Carcinoma | 43 |
| Chapter 4: Effect of HCV clearance with direct act antiviral agents on HCC | ing 55 |
| Patients and Methods | 58 |
| Results | 68 |
| Discussion | 80 |
| Conclusion | 87 |
| Recommendations | 88 |
| References | 89 |
| Arabic Summary | |

List of abbreviations

| AASLD | American Association for the Study of Liver |
|-------|---|
| | Diseases |
| AFP | Alpha-Feto Protein |
| ART | Anti-retroviral therapy |
| BCLC | Barcelona-Clinic Liver Cancer |
| CBP | Child bearing period |
| CD34 | Cluster of Differentiation 34 |
| CDC | Centers for Disease Control |
| CK7 | Cytokertain 7 |
| CKD | Chronic Kidney Disease |
| CLIP | Cancer of the Liver Italian Program |
| DAAs | Direct Acting Antivirals |
| DAC | Daclatasvir |
| DDIs | Drug drug interactions |
| EASL | European Association for the Study of the Liver |
| ECOG | Eastern Cooperative Oncology Group |
| EDHS | Egyptian Demographic Health Survey |
| eGFR | Estimated glomerular filteration rate |
| EHIS | Egyptian Health Issues Survey |
| EIA | Enzyme immunoassay |
| ER | Endoplasmic Reticulum |
| ESCRT | Endosomal-Sorting Complex Required for |
| | Transport |
| FE | Fisher Exact |

| HCC | Hepatocellular Carcinoma |
|--------|---|
| HSP-70 | Heat shock protein 70 |
| IDSA | Infectious Diseases Society of America |
| IFN | Interferone |
| IL28B | Interleukin 28B |
| INR | International normalized ratio |
| ISDR | Interferon Sensitivity Determining Region |
| LDLT | Living Donor Liver Transplant |
| LDs | Lipid Droplets |
| LED | Ledipasvir |
| LRT | Locoregional therapy |
| MC | Monte Carlo |
| MELD | Model for End-stage liver Disease |
| MSM | men who have sex with men |
| NAT | nucleic acid testing |
| NNPIs | Non-nucleoside polymerase inhibitors |
| NTRs | Non-Translated Regions |
| OCLN | Occludin |
| OPTN | Organ Procurement and Transplantation |
| | Network |
| ORF | Open Reading Frame |
| PCR | Polymerase chain reaction |
| PEI | Percutaneous ethanol injection |
| PET | Positron emission tomography |
| PWID | people who inject drugs |
| RBV | Ribavirin |

| RCT | Randomized control trial |
|-------|--|
| RDTs | Rapid diagnostic tests |
| RFA | Radiofrequency Ablation |
| ROS | Reactive Oxygen Species |
| SD | Standard deviation |
| SIM | Simeprevir |
| SOF | Sofosbuvir |
| SRB 1 | Scavenger Receptor B1 |
| SVR | Sustained Virological Response |
| TACE | Transcatheter arterial chemoembolization |
| TGF- | Transforming Growth Factor beta |
| beta. | |
| TNM | Tumor, node, and metastases |
| VIP | Vasoactive Intestinal peptide |
| WHO | World Health Organization |

List of Figures

| Fig. | Title | Page |
|------|---|------|
| 1 | Global epidemiology of hepatitis C virus | 4 |
| | infection | |
| 2 | Model of hepatitis C virus lipoviral particle | 7 |
| 3 | HCV genome and proteins | 8 |
| 4 | Natural history of HCV infection | 18 |
| 5 | DAAs mechanism of action & therapeutic target | 24 |
| 6 | Natural history and biological drivers of HCV | 45 |
| | induced HCC | |
| 7 | Contrast enhanced CT showing typical features | 47 |
| | of HCC | |
| 8 | MRI of a patient with HCC | 47 |
| 9 | Diagnostic algorithm and recall policy for | 49 |
| | hepatic nodules in cirrhotic patients | |
| 10 | Modified BCLC staging system and treatment | 52 |
| | strategy | |
| 11 | Incidence of HCC in HCV-associated cirrhosis | 57 |
| | according to different treatment strategies | |
| 12 | Ultrasound device | 62 |
| 13 | Concordance between liver stiffness (kPa) and | 63 |
| | fibrosis stage according to METAVIR score in | |
| | chronic HCV patients. | |
| 14 | Describes and compares both groups regarding | 71 |
| | serum Albumin, Total bilirubin and INR before | |

| | starting treatment | |
|-----|---|---------|
| 4 - | | |
| 15 | Before treatment comparison between DAA | 73 |
| | receiving and control patients regarding | |
| | different stages of hepatic fibrosis determined | |
| | by transient elastography | |
| 16 | Comparison between HCC incidence in two | 74 |
| | groups | |
| 17 | Comparison between two DAA subgroups | 76 |
| | regarding serum Albumin, Total bilirubin and | |
| | INR before starting treatment. | |
| 18 | Comparison between 2 DAA subgroups with | 77 |
| | and without HCC after treatment regarding | |
| | previous exposure to DAA before study | |
| 19 | Comparison between patients with no incidence | 78 |
| | of HCC and those with HCC after receiving | |
| | DAA regarding prevalence of ascites, | |
| | splenomegaly and esophageal varices | |
| 20 | Comparison between patients with no incidence | 79 |
| | of HCC and those with HCC after receiving | |
| | DAA regarding different hepatic fibrosis stages | |
| | using transient elastography | |

List of Tables

| Table | Title | Page |
|-------|--|------|
| 1 | Eastern Cooperative Oncology Group | 50 |
| | (ECOG, Zubrod, WHO) performance scale | |
| 2 | Comparison between DAA receiving group | 69 |
| | and control group regarding age and | |
| | different laboratory values before starting | |
| | treatment. | |
| 3 | Comparison between DAA receiving and | 72 |
| | non-receiving patients. Regarding | |
| | prevalence of ascites, splenomegaly, and | |
| | esophageal varices. | |
| 4 | Before treatment comparison between DAA | 73 |
| | receiving and non-receiving patients | |
| | regarding different stages of hepatic fibrosis | |
| | determined by transient elastography | |
| 5 | Comparison between HCC incidence in | 74 |
| | patients who received DAA and control | |
| | group | |
| 6 | Comparison between 2 DAA subgroups | 75 |
| | with and without HCC after treatment | |
| | regarding age and different laboratory | |
| | findings before receiving treatment. | |
| 7 | Comparison between 2 DAA subgroups | 77 |
| | with and without HCC after treatment | |
| | regarding previous exposure to DAA before | |

| Table | Title | Page |
|-------|--|------|
| | study | |
| 8 | Comparison between patients with no incidence of HCC and those with HCC after receiving DAA regarding prevalence of ascites, splenomegaly and esophageal varices | 78 |
| 9 | Comparison between patients with no incidence of HCC and those with HCC after receiving DAA regarding different hepatic fibrosis stages using transient elastography | 79 |

Abstract

Background: Significant advances in understanding of the molecular virology, life cycle, and pathogenesis of Hepatitis C Virus (HCV) led to the Direct-Acting Anti-viral (DAA) era of HCV therapy in 2011. It can be expected that rates of HCV-associated hepatocellular carcinoma (HCC) will decrease significantly after the widespread adoption of DAAs, However Hepatitis C patients with cirrhosis who were treated with direct-acting antivirals had increased likelihood of developing HCC. HCC was also associated with greater liver stiffness according to transient elastography and lower platelet counts. The aim of this study is to investigate incidence of HCC in Egyptian HCV patients in whom other predominant HCV genotypes are prevalent and different treatment protocols followed.

Methods: This was a retrospective study including 400 chronic HCV patients who were following up their medical condition at Kobri El-Koba Military Hospital hepatology outpatient clinic from January 2018 to September 2019. Patients were divided into two main equal groups regarding either received HCV direct acting antivirals or not. Incidence of HCC after 18 months of follow up were compared between two groups. Its relation to hepatic fibrosis stage was calculated in both groups.

Results: DAA receiving group had significantly lower incidence of HCC than non DAA receiving group (control group). Eleven patients in DAA receiving group developed HCC (5.5%) compared to twenty-two patients in control group (11%) with P- value 0.04. Although there was no significant difference between two groups regarding pre-treatment prevalence of ascites, splenomegaly, or esophageal varices, DAA receiving group had statistically significant advanced hepatic fibrosis when compared to control group. Before starting treatment, DAA Receiving group shows (4.5% F0, 14% F1, 7% F2, 11.5% F3 and 63% F4) versus (20.5% F0, 14% F1, 18.5% F2, 6.5% F3 and 40.5% F4) in control group with highly significant P value 0.00.

Conclusion: Incidence of HCC decreased significantly after DAA in chronic HCV patients. Decreased incidence occurred despite advanced hepatic fibrosis in this group of patients.

Key words: Hepatocellular carcinoma- Direct acting antivirals - Hepatitis C virus